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     (FILE 'HOME' ENTERED AT 07:34:49 ON 30 MAR 2001)
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     FILE 'REGISTRY' ENTERED AT 07:34:57 ON 30 MAR 2001
               E CEFUROXIME AXETIL/CN
L1             1 S E3
               E C20H22N4O10S/MF
L2            16 S E3 AND NC3-NCSC3/ES AND OC4/ES
L3            15 S L2 NOT 3 FURANYL
L4            13 S L3 NOT 2 2 FURANYL
L5            12 S L4 NOT DIMETHYL 2 OXOETHOXY
L6            11 S L5 NOT OXOPROPOXY
L7            10 S L6 NOT 2 ACETYLOXY
L8            10 S L1,L7

     FILE 'HCAPLUS' ENTERED AT 07:41:09 ON 30 MAR 2001
L9           248 S L8
L10          268 S CEFUROXIME AXETIL#
L11            3 S ELOBACT OR CEFTIN#
L12            4 S CEFUROXIMEAXETIL? OR CEFUROXIMAXETIL?
L13          291 S L9-L12
L14          201 S L13 AND (PD<=19970815 OR PRD<=19970815 OR AD<=19970815 OR PY<
               E SHERMAN B/AU
L15           48 S E3,E17-E20
L16            3 S L13 AND L15

     FILE 'REGISTRY' ENTERED AT 07:48:57 ON 30 MAR 2001
L17            1 S 67-64-1
               SEL RN L8
L18            1 S E1-E10/CRN

     FILE 'HCAPLUS' ENTERED AT 07:49:21 ON 30 MAR 2001
L19            1 S L18
L20          202 S L19,L14
L21            1 S L15 AND L20
L22            3 S L16,L21
L23            4 S L20 AND (L17 OR ACETONE)

     FILE 'REGISTRY' ENTERED AT 07:51:39 ON 30 MAR 2001
L24            1 S 9003-39-8
L25            1 S 9004-64-2
L26            1 S 9004-67-5
L27            1 S 63-42-3
L28            1 S 69-65-8
L29            3 S 50-70-4 OR 6706-59-8 OR 26566-34-7
L30            1 S 74811-65-7
L31            1 S 9063-38-1
L32            1 S 57-11-4

     FILE 'HCAPLUS' ENTERED AT 07:52:49 ON 30 MAR 2001
L33            2 S L20 AND (L24 OR POVIDONE OR CROSPOVIDONE OR CROS POVIDONE)
L34            3 S L20 AND (L25 OR HYDROXYPROPYLCELLULOS? OR HYDROXYPROPYL CELLU
L35            4 S L20 AND (L26 OR METHYLCELLULOS? OR METHYL CELLULOS?)
L36            3 S L20 AND (L27 OR LACTOSE)
L37            2 S L20 AND (L28 OR MANNITOL)
L38            1 S L20 AND (L29 OR SORBITOL)
L39            1 S L20 AND (L30 OR CROSCARMELOS?(A)(SODIUM OR NA))
L40            2 S L20 AND (L30 OR CROSCARMELLOS?(A)(SODIUM OR NA))
L41            2 S L20 AND (CROSCARMELLOS? OR CROSCARMELOS?)
L42            1 S L20 AND (L31 OR (NA OR SODIUM)()STARCH(L)GLYCOLATE)
L43            9 S L20 AND (L32 OR STEARIC ACID OR STEARATE)
L44            1 S L23 AND L33-L43
L45            4 S L23,L44
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Point of Contact:
Jan D[illegible]
Librarian-Phy[illegible]ences
CM1 1E01 Tel: 308-4498

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L46           4 S L43 AND L33-L42,L23
L47           9 S L22,L23,L45,L46
L48          12 S L33-L42,L44,L47

     FILE 'REGISTRY' ENTERED AT 07:58:07 ON 30 MAR 2001
L49           1 S CELLULOSE/CN
L50        5957 S 9004-34-6/CRN

     FILE 'HCAPLUS' ENTERED AT 07:58:20 ON 30 MAR 2001
L51           7 S L49,L50 AND L20
L52          13 S L48,L51

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FILE LAST UPDATED: 29 Mar 2001  (20010329/ED)

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L52  ANSWER 1 OF 13  HCAPLUS  COPYRIGHT 2001 ACS
AN   2001:133640  HCAPLUS
DN   134:183492
TI   Stabilized cefuroxime axetil
IN   Sherman, Bernard Charles
PA   Can.
SO   Eur. Pat. Appl., 6 pp.
     CODEN: EPXXDW
DT   Patent
LA   English
IC   ICM  A61K031-545
     ICS  A61K009-16; A61K009-20
CC   63-6 (Pharmaceuticals)
FAN.CNT 1
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
PI   EP 1077067         A1   20010221      EP 2000-306380   20000727
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
PRAI CA 1999-2280925  19990729
AB   Solid pharmaceutical compns. comprise cefuroxime axetil
     as active ingredient and a zinc salt as stabilizer.  A compn. contained
```

cefuroxime axetil 90, sorbitol 9.6, ZnCl2 0.4, acetone 400, and water 100.

ST **cefuroxime axetil** stabilized zinc salt

IT Drug delivery systems
(granules; zinc salts stabilization of **cefuroxime axetil**)

IT Drug delivery systems
(powders; zinc salts stabilization of **cefuroxime axetil**)

IT Drug delivery systems
(suspensions, oral; zinc salts stabilization of **cefuroxime axetil**)

IT Drug delivery systems
(tablets; zinc salts stabilization of **cefuroxime axetil**)

IT 7440-66-6D, Zinc, salts 7646-85-7, Zinc chloride, biological studies **64544-07-6, Cefuroxime axetil**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(zinc salts stabilization of **cefuroxime axetil**)

RE.CNT 1

RE

(1) Access Pharmaceuticals; EP 0872248 A 1998 HCAPLUS

L52 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2001 ACS

AN 1999:783971 HCAPLUS

DN 132:15666

TI **Cefuroxime axetil** tablets formulations

IN **Sherman, Bernard Charles**

PA Can.

SO PCT Int. Appl., 11 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K047-02
ICS A61K031-545

CC 63-6 (Pharmaceuticals)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9962559	A1	19991209	WO 1999-CA446	19990518
	W: AU, BR, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9938074	A1	19991220	AU 1999-38074	19990518
PRAI	CA 1998-2239331		19980529		
	WO 1999-CA446		19990518		

AB A pharmaceutical tablet comprising **cefuroxime axetil** and a carbonate or bicarbonate. Thus, **cefuroxime axetil** (4.5 kg) together with 0.5 kg of sorbitol were dissolved in a mixt. of 20.0 kg of acetone and 5.0 kg of water. The soln. was spray-dried to obtain a co-ppt. comprising by wt. 90% **cefuroxime axetil** and 10% sorbitol. About 0.4% by wt. magnesium stearate, as a lubricant, and 0.1% by wt. colloidal silicon dioxide, as glidant, were added to this coppt. and the mixt. was then compacted to increase its d. and then ground up into granules. The following compn. was prepd. from granules 3500, crospovidone 1470, sodium bicarbonate 700, magnesium stearate 20, and colloidal silicon dioxide 10 g. This mixt. was then compressed into tablets each weighing 1140 mg. Each tablet contained about 627 mg of **cefuroxime axetil**, which in turn is equiv. to about 500 mg cefuroxime.

ST **cefuroxime axetil** tablet formulation

IT Bicarbonates
Carbonates, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cefuroxime axetil** tablet formulations)

IT Drug delivery systems
(tablets; **cefuroxime axetil** tablet formulations)
IT 144-55-8, Carbonic acid monosodium salt, biological studies 471-34-1, Calcium carbonate, biological studies 497-19-8, Sodium carbonate, biological studies 546-93-0, Magnesium carbonate 584-08-7 9003-39-8, PVP 9063-38-1, Sodium starch glycolate **64544-07-6**, **Cefuroxime axetil** 74811-65-7, Croscarmellose sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cefuroxime axetil** tablet formulations)
RE.CNT 4
RE
(1) Charles, S; WO 9908683 A 1999 HCAPLUS
(2) Crisp, H; US 4820833 A 1989 HCAPLUS
(3) Deutsch, D; US 4897270 A 1990 HCAPLUS
(4) Glaxo Group Ltd; GB 2126479 A 1984 HCAPLUS

L52 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:141215 HCAPLUS
DN 130:187203
TI Pharmaceutical compositions comprising coprecipitates of **cefuroxime axetil** and water-soluble excipients
IN **Sherman, Bernard Charles**
PA Can.
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-545
ICS A61K009-14; A61K009-20
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9908683	A1	19990225	WO 1998-CA773	19980807 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9888470	A1	19990308	AU 1998-88470	19980807 <--
EP 996449	A1	20000503	EP 1998-940001	19980807 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI CA 1997-2209868 19970815 <--
WO 1998-CA773 19980807
AB Disclosed is a coppt. of **cefuroxime axetil** and a water-sol. excipient. Process for making the coppt., and pharmaceutical compns. contg. the coppt. for oral administration are also disclosed. A coppt. contg. **cefuroxime axetil** and **hydroxypropyl cellulose** at 10:1 was prepd. by spray drying the **acetone**/methanol soln. The coppt. 134.2 g was combined with **croscarmellose Na** 44, Mg **stearate** 1, and colloidal SiO2 0.8 g to make tablets contg. cefuroxime 500 mg in each. The tablets exhibited in vitro dissoln. profile when measured according to U.S. Pharmacopeia XXIII (USP) as follows; cefuroxime .apprx.65 % was released in 20 min and .apprx.90 % in 60 min, which complied with the USP specification.
ST **cefuroxime axetil** cellulose coppt tablet dissoln
IT Aggregates
(coacervates; prodn. of coppts. contg. **cefuroxime axetil** and water-sol. excipients for oral pharmaceuticals)
IT Tablets (drug delivery systems)
(tablets contg. coppts. of **cefuroxime axetil** and

water-sol. excipients)
IT **57-11-4, Stearic acid**, biological studies
557-04-0, Magnesium **stearate**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lubricant; tablets contg. coppts. of **cefuroxime axetil** and water-sol. excipients)
IT **67-64-1, Acetone**, uses
RL: NUU (Nonbiological use, unclassified); USES (Uses)
(prodn. of coppts. contg. **cefuroxime axetil** and water-sol. excipients for oral pharmaceuticals)
IT **50-70-4, Sorbitol**, biological studies **63-42-3, Lactose 69-65-8, Mannitol 9003-39-8, Povidone 9004-64-2, Hydroxypropyl cellulose 9004-67-5, Methyl cellulose 64544-07-6, Cefuroxime axetil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tablets contg. coppts. of **cefuroxime axetil** and water-sol. excipients)
IT **9063-38-1, Sodium starch glycolate 74811-65-7, Croscarmellose sodium**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tablets contg. coppts. of **cefuroxime axetil** and water-sol. excipients and disintegrant)
RE.CNT 8
RE
(1) ACS Dobfar SPA, Milan (IT); EP 0757991 A 1997 HCAPLUS
(2) BASF; EP 0821965 A 1998 HCAPLUS
(3) Eli Lilly and Co, USA; EP 0280571 A 1988 HCAPLUS
(4) Glaxo; EP 0107276 A 1984 HCAPLUS
(5) Glaxo; FR 2549837 A 1985 HCAPLUS
(6) Glaxo; GB 2181052 A 1987 HCAPLUS
(7) Glaxo; GB 2204792 A 1988 HCAPLUS
(8) Yissum Res Dev Co, IL; WO 9822091 A 1998 HCAPLUS

L52 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:351747 HCAPLUS
DN 129:45322
TI Pharmaceutical preparations for the controlled release of .beta.-lactam antibiotics
IN Katzhendler, Ifat; Hoffman, Amnon; Friedman, Michael
PA Yissum Research Development Company of the Hebrew, Israel; Katzhendler, Ifat; Hoffman, Amnon; Friedman, Michael
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-10
ICS A61K009-22; A61K009-24; A61K009-26; A61K009-66; A61K047-32; A61K047-36; A61K047-38; A61K047-42; A61K047-44
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9822091	A1	19980528	WO 1997-I	
L368 19971113 <--				
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9748825	A1	19980610	AU 1997-48825	19971113 <--
EP 941064	A1	19990915	EP 1997-911421	19971113 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, FI
PRAI IL 1996-119627 19961117 <--
WO 1997-I
L368 19971113
AB The present invention relates to a pharmaceutical controlled-release oral drug delivery system comprising as active ingredient at least one .beta.-lactam antibiotic agent, having a specific absorption site in the small intestine in combination with a polymeric matrix, optionally further contg. addnl. pharmaceutically acceptable constituents, wherein at least 50 % of the .beta.-lactam antibiotic agent are released from the matrix within 3-4 h from oral administration and the remainder of the pharmaceutical agent is released at a controlled rate. The drug delivery system optionally further comprises a .beta.-lactamase inhibitor, preferably in combination with amoxicillin and/or amoxicillin trihydrate as the active ingredient. The polymeric matrix of the pharmaceutical controlled-release oral drug delivery system may be of hydrophilic and/or hydrophobic nature and the delivery system may further comprise pharmaceutically acceptable additive. The pharmaceutical controlled-release oral drug delivery system of the invention is preferably in dosage unit form. A tablet contained amoxicillin.cntdot.3H2O 603.75, Methocel K100 LV 120.75, Avicel PH101 55.5, Mg **stearate** 10, and Aerosil 200 0 mg.
ST controlled release tablet lactam antibiotic matrix; amoxicillin Methocel controlled release tablet
IT Beeswax
Capsules (drug delivery systems)
Drug bioavailability
Tablets (drug delivery systems)
.beta.-Lactam antibiotics
(controlled-release oral prepns. contg. .beta.-lactam antibiotics in combination with polymeric matrix)
IT Albumins, biological studies
Carnauba wax
Hydrogenated castor oil
Polyamides, biological studies
Serum albumin
Soybean proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release oral prepns. contg. .beta.-lactam antibiotics in combination with polymeric matrix)
IT 9073-60-3, .beta.-Lactamase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(controlled-release oral prepns. contg. .beta.-lactam antibiotics in combination with polymeric matrix)
IT 61-33-6, Penicillin G, biological studies 61-72-3, Cloxacillin 66-79-5, Oxacillin 69-53-4, Ampicillin 87-08-1, Penicillin V 112-92-5, 1-Octadecanol 147-52-4, Nafcillin 3116-76-5, Dicloxacillin 9003-05-8, Polyacrylamide **9004-32-4**, Sodium carboxymethyl cellulose **9004-62-0**, Hydroxyethyl cellulose **9004-64-2**, **Hydroxypropyl cellulose 9004-65-3** **9004-67-5, Methyl cellulose** 9005-38-3, Sodium alginate 9012-76-4, Chitosan **9032-42-2**, Hydroxyethyl **methyl cellulose** 9036-66-2, Arabinogalactan 15686-71-2, Cefalexin 25086-15-1, Eudragit S100 26787-78-0, Amoxicillin 29593-61-1, Glycerol palmitostearate 31566-31-1 35607-66-0, Cefoxitin 50370-12-2, Cefadroxil 53994-73-3, Cefaclor 55268-75-2, Cefuroxime 61336-70-7, Amoxicillin trihydrate **64544-07-6, Cefuroxime axetil** 79350-37-1, Cefixime 80210-62-4, Cefpodoxime 87239-81-4, Cefpodoxime proxetil 92665-29-7, Cefprozil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release oral prepns. contg. .beta.-lactam antibiotics in combination with polymeric matrix)
IT 58001-44-8 68373-14-8, Sulbactam
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-lactamase inhibitor; controlled-release oral prepns. contg.

.beta.-lactam antibiotics in combination with polymeric matrix)

L52 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:293427 HCAPLUS
DN 129:8597
TI Embedding and encapsulation of controlled release particles
IN Van Lengerich, Bernhard H.
PA Van Lengerich, Bernhard H., USA
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM B29C047-04
ICS B01J013-04; A01N025-26
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 5
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9818610	A1	19980507	WO 1997-US18984	19971027 <--
	W: AU, CA, JP, NO, PL, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9749915	A1	19980522	AU 1997-49915	19971027 <--
	EP 935523	A1	19990818	EP 1997-912825	19971027 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	NO 9902036	A	19990428	NO 1999-2036	19990428 <--
PRAI	US 1996-29038	19961028 <--			
	US 1997-52717	19970716 <--			
	WO 1997-US18984	19971027			

AB Controlled release, discrete, solid particles which contain an encapsulated and/or embedded component such as a heat sensitive or readily oxidizable pharmaceutically, biol., or nutritionally active component are continuously produced without substantial destruction of the matrix material or encapsulant. A release-rate controlling component is incorporated into the matrix to control the rate of release of the encapsulant from the particles. The addnl. component may be a hydrophobic component or a high water binding capacity component for extending the release time. The plasticizable matrix material, such as starch, is admixed with at least one plasticizer, such as water, and at least one release-rate controlling component under low shear mixing conditions to plasticize the plasticizable material without substantially destroying the at least one plasticizable material and to obtain a substantially homogeneous plasticized mass. The plasticizer content is substantially reduced and the temp. of the plasticized mass is substantially reduced prior to admixing the plasticized mass with the encapsulant to avoid substantial destruction of the encapsulant and to obtain a formable, extrudable mixt. The mixt. is extruded though a die without substantial or essentially no expansion and cut into discrete, relatively dense particles. Release properties may also be controlled by precoating the encapsulant and/or coating the extruded particles with a film-forming component. An example of encapsulation of acetylcysteine is given using starch, polyethylene, glycerol monostearate, and vegetable oil.

ST encapsulation controlled release particle

IT Antitumor agents
Antiviral agents
Controlled release drug delivery systems
Encapsulation
(embedding and encapsulation of controlled release particles)

IT Estrogens
Polyoxyalkylenes, biological studies
Tuberculin
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(embedding and encapsulation of controlled release particles)

IT Antibiotics

Antioxidants
Detergents
Emulsifying agents
Extrusion (nonbiological)
Fats and Glyceridic oils, biological studies
Fatty acids, biological studies
Flavor
Fungicides
Glass transition
Heat treatment
Herbicides
Hydrocolloids
Insecticides
Lipids, biological studies
Monoclonal antibodies
Paraffin waxes, biological studies
Peptides, biological studies
Perfumes
Pesticides
Plasticizers
Polyolefins
Polyurethanes, biological studies
Proteins (general), biological studies
Rodenticides
Steroids, biological studies
Surfactants
Waxes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(embedding and encapsulation of controlled release particles)

IT Drug delivery systems
(particles; embedding and encapsulation of controlled release particles)

IT 50-02-2, Dexamethasone 50-04-4, Cortisone acetate 50-06-6, Phenobarbital, biological studies 50-12-4, Mephenytoin 50-14-6, Ergocalciferol 50-18-0, Cyclophosphamide 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-27-1, Estriol 50-28-2, Estradiol, biological studies 50-33-9, Phenylbutazone, biological studies 50-36-2, Cocaine 50-41-9, Clomiphene citrate 50-44-2, Mercaptopurine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 50-54-4, Quinidine sulfate 50-55-5, Reserpine 50-58-8, Phendimetrazine tartrate 50-63-5, Chloroquine phosphate 50-78-2, Acetylsalicylic acid 50-81-7, Ascorbic acid, biological studies 50-96-4, Isoetharine hydrochloride 51-05-8, Procaine hydrochloride 51-15-0, Pralidoxime chloride 51-21-8, Fluorouracil 51-30-9, Isoproterenol hydrochloride 51-34-3, Scopolamine 51-43-4, Epinephrine 51-48-9, Levothyroxine, biological studies 51-52-5, Propylthiouracil 51-55-8, Atropine, biological studies 51-57-0, Methamphetamine hydrochloride 51-64-9, Dextroamphetamine 51-83-2, Carbachol 51-84-3, Acetylcholine, biological studies 51-98-9, Norethindrone acetate 52-01-7, Spironolactone 52-24-4, Thiotepa 52-49-3, Trihexyphenidyl hydrochloride 52-53-9, Verapamil 52-67-5, Penicillamine 52-68-6, Trichlorfon 52-86-8, Haloperidol 52-89-1, Cysteine hydrochloride 53-03-2, Prednisone 53-16-7, Estrone, biological studies 53-19-0, Mitotane 53-39-4, Oxandrolone 53-60-1, Promazine hydrochloride 53-86-1, Indomethacin 54-21-7, Sodium salicylate 54-31-9, Furosemide 54-36-4, Metyrapone 54-64-8, Thimerosal 54-85-3, Isoniazid 55-03-8, Levothyroxine sodium 55-06-1, Liothyronine sodium 55-63-0, Nitroglycerin 55-98-1, Busulfan 56-29-1, Hexobarbital 56-47-3, Desoxycorticosterone acetate 56-53-1, Diethylstilbestrol 56-54-2, Quinidine 56-75-7, Chloramphenicol 56-84-8, L-Aspartic acid, biological studies 56-87-1, L-Lysine, biological studies 57-13-6, Urea, biological studies 57-22-7, Vincristine 57-33-0, Pentobarbital sodium 57-41-0, Phenytoin 57-42-1, Meperidine 57-43-2, Amobarbital 57-47-6, Physostigmine 57-53-4, Meprobamate 57-63-6, Ethinyl estradiol 57-66-9, Probenecid 57-68-1, Sulfamethazine 57-83-0, Progesterone, biological studies

57-92-1, Streptomycin, biological studies 57-96-5, Sulfinpyrazone 58-00-4, Apomorphine 58-08-2, Caffeine, biological studies 58-14-0, Pyrimethamine 58-18-4, Methyltestosterone 58-22-0 58-25-3, Chlordiazepoxide 58-27-5, Menadione 58-32-2, Dipyridamole 58-33-3, Promethazine hydrochloride 58-38-8, Prochlorperazine 58-39-9, Perphenazine 58-40-2, Promazine 58-54-8, Ethacrynic acid 58-55-9, Theophylline, biological studies 58-56-0, Pyridoxine hydrochloride 58-85-5, Biotin 58-89-9, Lindane 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-05-2, Methotrexate 59-30-3, Folic acid, biological studies 59-33-6, Pyrilamine maleate 59-43-8, Thiamin, biological studies 59-52-9, Dimercaprol 59-63-2, Isocarboxazid 59-66-5, Acetazolamide 59-67-6, Niacin, biological studies 59-92-7, Levodopa, biological studies 60-13-9, Amphetamine sulfate 60-18-4, Tyrosine, biological studies 60-54-8, Tetracycline 60-56-0, Methimazole 60-80-0, Antipyrine 60-87-7, Promethazine 60-99-1, Levomepromazine 61-00-7, Acepromazine 61-25-6, Papaverine hydrochloride 61-68-7, Mefenamic acid 61-76-7, Phenylephrine hydrochloride 61-90-5, Leucine, biological studies 62-31-7, Dopamine hydrochloride 62-44-2, Phenacetin 62-67-9, Nalorphine 62-90-8, Nandrolone phenpropionate 63-68-3, Methionine, biological studies 63-91-2, Phenylalanine, biological studies 63-92-3, Phenoxybenzamine hydrochloride 63-98-9, Phenacemide 64-31-3, Morphine sulfate 64-72-2, Chlortetracycline hydrochloride 64-77-7, Tolbutamide 64-86-8, Colchicine 65-45-2, Salicylamide 66-76-2, Dicoumarol 67-03-8, Thiamine hydrochloride 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 67-73-2, Fluocinolone acetonide 67-96-9, Dihydrotachysterol 67-97-0, Cholecalciferol 68-19-9, Cyanocobalamin 68-22-4, Norethindrone 68-35-9, Sulfadiazine 68-41-7, Cycloserine 68-89-3, Metamizole 69-23-8, Fluphenazine 69-44-3, Amodiaquine hydrochloride 69-53-4, Ampicillin 69-72-7, Salicylic acid, biological studies 71-00-1, Histidine, biological studies 71-58-9, Medroxyprogesterone acetate 71-63-6, Digitoxin 71-68-1, Hydromorphone hydrochloride 71-81-8 72-14-0, Sulfathiazole 72-17-3, Sodium lactate 72-18-4, Valine, biological studies 72-19-5, L-Threonine, biological studies 72-33-3, Mestranol 72-63-9, Methandrostenolone 73-22-3, L-Tryptophan, biological studies 73-48-3, Bendroflumethiazide 76-38-0, Methoxyflurane 76-42-6, Oxycodone 76-43-7, Fluoxymesterone 76-57-3, Codeine 77-09-8 77-19-0, Dicyclomine 77-21-4, Glutethimide 77-26-9, Butalbital 77-27-0, Thiamylal 77-36-1, Chlorthalidone 77-41-8, Methsuximide 78-44-4, Carisoprodol 79-57-2, Oxytetracycline 80-08-0, Dapsone 80-13-7, Halazone 80-53-5, Terpin 81-07-2, Saccharin 81-13-0, Dexpanthenol 81-23-2, Dehydrocholic acid 81-81-2, Warfarin 83-43-2, Methylprednisolone 83-73-8, Iodoquinol 83-88-5, Riboflavin, biological studies 84-02-6, Prochlorperazine maleate 84-17-3, Dienestrol 84-22-0, Tetrahydrozoline 84-80-0, Phytonadione 85-79-0, Dibucaine 86-35-1, Ethotoin 87-00-3, Homatropine 87-08-1, Phenoxymethylpenicillin 87-33-2, ISDN 89-57-6, 5-Aminosalicylic acid 90-33-5, Hymecromone 90-34-6, Primaquine 91-33-8, Benzthiazide 91-81-6, Tripelennamine 92-13-7, Pilocarpine 93-14-1, Guaifenesin 94-09-7, Benzocaine 94-20-2, Chlorpropamide 95-25-0, Chlorzoxazone 97-53-0, Eugenol 97-77-8, Disulfiram 98-96-4, Pyrazinamide 99-66-1, Valproic acid 100-97-0, biological studies 101-26-8, Pyridostigmine bromide 101-31-5, Hyoscyamine 102-76-1, Triacetin 103-16-2, Monobenzone 103-86-6, Hydroxyamphetamine 103-90-2, Acetaminophen 104-28-9, Cinoxate 104-31-4, Benzonatate 107-43-7, Betaine 108-46-3, 1,3-Benzenediol, biological studies 110-85-0, Piperazine, biological studies 110-94-1, Pentanedioic acid 113-18-8, Ethchlorvynol 113-52-0, Imipramine hydrochloride 113-59-7, Chlorprothixene 113-92-8, Chlorpheniramine maleate 114-07-8, Erythromycin 114-80-7, Neostigmine bromide 115-38-8, Mephobarbital 115-77-5, biological studies 120-97-8, Dichlorphenamide 121-25-5, Amprolium 121-54-0
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(embedding and encapsulation of controlled release particles)

IT 121-75-5, Malathion 123-31-9, 1,4-Benzenediol, biological studies 124-90-3, Oxycodone hydrochloride 124-94-7, Triamcinolone 125-28-0,

Dihydrocodeine 125-33-7, Primidone 125-71-3, Dextromethorphan 125-72-4, Levorphanol tartrate 126-07-8, Griseofulvin 127-07-1, Hydroxyurea 127-33-3, Demeclocycline 127-48-0, Trimethadione 127-69-5, Sulfisoxazole 127-79-7, Sulfamerazine 128-44-9, Saccharin sodium 128-46-1, Dihydrostreptomycin 128-49-4, Docusate calcium 128-62-1, Noscapine 129-20-4, Oxyphenbutazone 129-49-7, Methysergide maleate 129-51-1, Ergonovine maleate 130-26-7, Clioquinol 130-61-0, Thioridazine hydrochloride 131-13-5 131-57-7, Oxybenzone 132-17-2 132-92-3, Methicillin sodium 133-58-4, Nitromersol 133-67-5, Trichlormethiazide 134-03-2, Sodium ascorbate 134-80-5, Diethylpropion hydrochloride 135-07-9 135-09-1, Hydroflumethiazide 136-40-3, Phenazopyridine hydrochloride 136-47-0 136-77-6, Hexylresorcinol 137-58-6, Lidocaine 141-01-5, Ferrous fumarate 143-71-5, Hydrocodone bitartrate 143-81-7, Butabarbital sodium 144-14-9, Anileridine 144-48-9, Iodoacetamide 144-55-8, Sodium bicarbonate, biological studies 144-80-9, Sulfacetamide 144-82-1, Sulfamethizole 144-83-2, Sulfapyridine 146-22-5, Nitrazepam 146-54-3, Triflupromazine 147-24-0, Diphenhydramine hydrochloride 147-52-4, Nafcillin 147-85-3, Proline, biological studies 148-79-8 148-82-3, Melphalan 151-67-7, Halothane 152-62-5, Dydrogesterone 152-97-6, Fluocortolone 154-41-6, Phenylpropanolamine hydrochloride 154-42-7, Thioguanine 156-51-4, Phenelzine sulfate 297-76-7, Ethynodiol diacetate 298-46-4, Carbamazepine 298-50-0, Propantheline 298-57-7, Cinnarizine 298-59-9, Methylphenidate hydrochloride 298-81-7, Methoxsalen 299-27-4, Potassium gluconate 299-29-6, Ferrous gluconate 299-42-3, Ephedrin 302-22-7, Chlormadinone acetate 302-79-4, Tretinoin 303-25-3, Cyclizine hydrochloride 304-20-1, Hydralazine hydrochloride 304-59-6, Potassium sodium tartrate 305-03-3, Chlorambucil 309-43-3, Secobarbital sodium 315-30-0, Allopurinol 317-34-0, Aminophylline 318-98-9 329-65-7, 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]- 343-55-5, Dicloxacillin sodium 345-78-8, Pseudoephedrine hydrochloride 346-18-9, Polythiazide 356-12-7, Fluocinonide 357-07-3, Oxymorphone hydrochloride 359-83-1, Pentazocine 360-70-3, Nandrolone decanoate 364-62-5, Metoclopramide 364-98-7, Diazoxide 366-70-1, Procarbazine hydrochloride 378-44-9, Betamethasone 379-79-3, Ergotamine tartrate 382-67-2, Desoximetasone 389-08-2, Nalidixic acid 390-64-7, Prenylamine 396-01-0, Triamterene 426-13-1, Fluorometholone 434-07-1, Oxymetholone 435-97-2, Phenprocoumon 437-74-1, Xantinol nicotinate 439-14-5, Diazepam 440-17-5, Trifluoperazine hydrochloride 443-48-1, Metronidazole 446-86-6, Azathioprine 465-65-6, Naloxone 466-99-9, Hydromorphone 471-34-1, Calcium carbonate, biological studies 474-86-2, Equilin 479-18-5, Dyphylline 484-23-1, Dihydralazine 486-12-4, Triprolidine 511-12-6, Dihydroergotamine 514-36-3, Fludrocortisone acetate 514-65-8, Biperiden 518-47-8, Fluorescein sodium 519-37-9, Etofylline 520-85-4, Medroxyprogesterone 523-87-5, Dimenhydrinate 525-66-6, Propranolol 527-07-1, Sodium gluconate 532-03-6, Methocarbamol 533-45-9, Clomethiazole 536-21-0, Norfenefrine 536-33-4, Ethionamide 541-15-1, Levocarnitine 546-88-3, Acetohydroxamic acid 546-93-0, Magnesium carbonate 548-62-9, Gentian violet 548-73-2, Droperidol 549-18-8, Amitriptyline hydrochloride 550-83-4, Propoxycaine hydrochloride 551-27-9, Propicillin 552-94-3, Salsalate 554-13-2, Lithium carbonate 554-57-4, Methazolamide 554-92-7, Trimethobenzamide hydrochloride 555-30-6, Methyldopa 557-34-6, Zinc acetate 562-10-7 564-25-0, Doxycycline 577-11-7, Docusate sodium 579-56-6, Isoxsuprine hydrochloride 587-61-1, Propyliodone 590-63-6, Bethanechol chloride 595-33-5, Megestrol acetate 596-51-0, Glycopyrrolate 599-79-1, Sulfasalazine 599-88-2, Sulfaperin 603-50-9, Bisacodyl 604-75-1, Oxazepam 614-39-1, Procainamide hydrochloride 616-91-1, Acetylcysteine 620-61-1, Hyoscyamine sulfate 630-56-8, Hydroxyprogesterone caproate 637-07-0, Clofibrate 637-58-1, Pramoxine hydrochloride 638-23-3 642-78-4, Cloxacillin sodium 651-06-9, Sulfamethoxydiazine 652-67-5 672-87-7, Metyrosine 709-55-7, Etilefrine 721-50-6, Prilocaine 723-46-6, Sulfamethoxazole 738-70-5, Trimethoprim 745-65-3, Alprostadil 747-36-4, Hydroxychloroquine sulfate 768-94-5, Amantadine 777-11-7, Haloprogin 797-63-7, Levonorgestrel 826-39-1, Mecamylamine

hydrochloride 846-49-1, Lorazepam 846-50-4, Temazepam 859-18-7, Lincomycin hydrochloride 865-21-4, Vinblastine 894-71-3, Nortriptyline hydrochloride 968-81-0, Acetohexamide 968-93-4, Testolacton 969-33-5, Cyproheptadine hydrochloride 985-16-0, Nafcillin sodium 1069-66-5, Sodium valproate 1070-11-7, Ethambutol hydrochloride 1077-28-7, Thioctic acid 1094-08-2, Ethopropazine hydrochloride 1095-90-5, Methadone hydrochloride 1098-97-1, Pyritinol 1104-22-9, Meclizine hydrochloride 1134-47-0, Baclofen 1143-38-0, Anthralin 1151-11-7, Ipodate calcium 1156-19-0, Tolazamide 1173-88-2, Oxacillin sodium 1197-21-3, Phentermine hydrochloride 1221-56-3, Ipodate sodium 1225-55-4, Protriptyline hydrochloride 1229-29-4, Doxepin hydrochloride 1247-42-3, Meprednisone 1263-89-4, Paromomycin sulfate 1309-48-4, Magnesium oxide, biological studies 1319-82-0, Aminocaproic acid 1321-23-9, Chloroxylenol 1343-97-1, Selenium sulfate 1393-48-2, Thiostrepton 1400-61-9, Nystatin 1403-17-4, Candicidin 1403-66-3, Gentamicin 1404-00-8, Mitomycin 1404-04-2, Neomycin 1404-88-2, Tyrothricin 1404-93-9, Vancomycin hydrochloride 1405-10-3, Neomycin sulfate 1405-20-5, Polymyxin b sulfate 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1406-05-9, Penicillin 1420-55-9, Thiethylperazine 1476-53-5, Novobiocin sodium 1492-18-8, Leucovorin calcium 1508-65-2, Oxybutynin chloride 1508-75-4, Tropicamide 1508-76-5, Procyclidine hydrochloride 1524-88-5, Flurandrenolide 1597-82-6, Paramethasone acetate 1617-90-9, Vincamine 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1639-60-7, Propoxyphene hydrochloride 1649-18-9, Azaperone 1668-19-5, Doxepin 1707-14-8, Phenmetrazine hydrochloride 1808-12-4, Bromodiphenhydramine hydrochloride 1812-30-2, Bromazepam 1897-96-7, Lonetil 1972-08-3, Dronabinol 1977-10-2, Loxapine 1982-37-2, Methdilazine 2013-58-3, Meclocycline
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IT 2022-85-7, Flucytosine 2030-63-9, Clofazimine 2062-78-4, Pimozide 2098-66-0, Cyproterone 2179-37-5, Bencyclane 2192-20-3, Hydroxyzine hydrochloride 2315-02-8, Oxymetazoline hydrochloride 2398-96-1, Tolnaftate 2438-32-6, Dexchlorpheniramine maleate 2447-57-6, Sulfadoxine 2589-47-1, Prajmalium bitartrate 2609-46-3, Amiloride 2709-56-0, Flupentixol 2898-12-6, Medazepam 2955-38-6, Prazepam 2998-57-4, Estramustine 3313-26-6, Thiothixene 3385-03-3, Flunisolide 3485-14-1, Cyclacillin 3485-62-9, Clidinium bromide 3486-35-9, Zinc carbonate 3505-38-2, Carbinoxamine maleate 3546-41-6, Pyrvinium pamoate 3572-43-8, Bromhexine 3575-80-2, Melperone 3625-06-7, Mebeverine 3632-91-5, Magnesium gluconate 3778-73-2, Ifosfamide 3810-80-8, Diphenoxylate hydrochloride 3902-71-4, Trioxsalen 3930-20-9, Sotalol 3963-95-9, Methacycline hydrochloride 3978-86-7, Azatadine maleate 4205-90-7, Clonidine 4205-91-8, Clonidine hydrochloride 4330-99-8, Trimeprazine tartrate 4468-02-4, Zinc gluconate 4498-32-2, Dibenzepine 4499-40-5, Oxtriphylline, biological studies 4697-36-3, Carbenicillin 4759-48-2, Isotretinoin 5051-62-7, Guanabenz 5104-49-4, Flurbiprofen 5321-32-4, Hetacillin potassium 5355-48-6 5370-01-4, Mexiletine hydrochloride 5534-09-8, Beclomethasone dipropionate 5536-17-4, Vidarabine 5636-83-9, Dimetindene 5638-76-6, Betahistine 5874-97-5, Metaproterenol sulfate 5875-06-9, Proparacaine hydrochloride 5987-82-6, Benoxinate hydrochloride 6202-23-9, Cyclobenzaprine hydrochloride 6284-40-8, Meglumine 6385-02-0, Meclofenamate sodium 6452-73-9, Oxprenolol hydrochloride 6493-05-6, Pentoxifylline 6533-00-2, Norgestrel 6805-41-0, Aescin 6890-40-0, Histamine phosphate 7054-25-3, Quinidine gluconate 7195-27-9, Mefruside 7235-40-7, .beta.-Carotene 7246-21-1, Tyropanoate sodium 7280-37-7, Estropipate 7297-25-8, Erythrityl tetranitrate 7414-83-7, Etidronate disodium 7439-95-4D, Magnesium, salts 7439-96-5, Manganese, biological studies 7439-96-5D, Manganese, salts 7440-39-3, Barium, biological studies 7440-69-9, Bismuth, biological studies 7440-70-2, Calcium, biological studies 7447-40-7, Potassium chloride (KCl), biological studies 7491-74-9, Piracetam 7553-56-2, Iodine, biological studies 7632-00-0, Sodium nitrite

7646-85-7, Zinc chloride, biological studies 7681-11-0, Potassium iodide (KI), biological studies 7681-49-4, Sodium fluoride, biological studies 7681-82-5, Sodium iodide, biological studies 7681-93-8, Natamycin 7693-13-2, Calcium citrate 7720-78-7, Ferrous sulfate 7778-49-6, Potassium citrate 7783-00-8, Selenious acid 7786-30-3, Magnesium chloride, biological studies 8017-57-0, Trisulfapyrimidine 8024-48-4, Casanthranol 8049-47-6, Pancreatin 8050-81-5, Simethicone 8065-29-0, Liotrix 8067-24-1, Ergoloid mesylates 9001-01-8, Kallidinogenase 9001-73-4, Papain 9002-07-7, Trypsin 9002-60-2, Corticotropin, biological studies 9002-61-3, Chorionic gonadotropin 9002-86-2, Pvc 9002-89-5, Polyvinyl alcohol 9003-20-7, Polyvinyl acetate **9003-39-8**, Pvp 9003-97-8, Polycarbophil 9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies **9004-32-4**, Carboxymethylcellulose **9004-34-6D**, Cellulose, esters and ethers 9004-53-9, Dextrin **9004-70-0**, Pyroxylin 9005-25-8, Starch, biological studies 9005-80-5, Inulin 9008-05-3, Histoplasmin 10025-73-7, Chromic chloride 10040-45-6, Sodium picosulfate 10238-21-8, Glibenclamide 10246-75-0, Hydroxyzine pamoate 10262-69-8, Maprotiline 10347-81-6, Maprotiline hydrochloride 10379-14-3, Tetrazepam 10418-03-8, Stanozolol 10540-29-1, Tamoxifen 11000-17-2, Vasopressin 12125-02-9, Ammonium chloride, biological studies 12619-70-4, Cyclodextrin 12622-73-0, Coccidioidin 12633-72-6, Amphotericin 12650-69-0, Mupirocin 13009-99-9, Mafenide acetate 13042-18-7, Fendiline 13292-46-1, Rifampin 13311-84-7, Flutamide 13392-18-2, Fenoterol 13422-51-0, Hydroxocobalamin 13463-67-7, Titanium dioxide, biological studies 13523-86-9, Pindolol 13614-98-7, Minocycline hydrochloride 13682-92-3, Dihydroxyaluminum aminoacetate 14009-24-6, Drotaverine 14028-44-5, Amoxapine 14779-78-3, Padimate 14976-57-9, Clemastine fumarate 15078-28-1, Nitroprusside 15307-86-5, Diclofenac 15622-65-8, Molindone hydrochloride 15663-27-1, Cisplatin 15676-16-1, Sulpiride 15686-51-8, Clemastine 15686-71-2, Cephalexin 15687-27-1 15687-41-9, Oxyfedrine 16482-55-6, Dihydroxyaluminum sodium carbonate 16595-80-5, Levamisole hydrochloride 16662-47-8, Gallopamil 17140-78-2, Propoxyphene napsylate 17230-88-5, Danazol 17560-51-9, Metolazone 17617-23-1, Flurazepam 18378-89-7, Plicamycin 18559-94-9, Salbutamol 19216-56-9, Prazosin 19237-84-4, Prazosin hydrochloride 19356-17-3, Calcifediol 20830-75-5, Digoxin 21462-39-5, Clindamycin hydrochloride 21738-42-1, Oxamniquine 21829-25-4, Nifedipine 22059-60-5, Disopyramide phosphate 22071-15-4, Ketoprofen 22195-34-2, Guanadrelsulfate 22204-24-6, Pyrantel pamoate 22204-53-1, Naproxen 22232-71-9, Mazindol 22260-51-1, Bromocriptine mesylate 22316-47-8, Clobazam 22494-42-4 22916-47-8 23031-25-6, Terbutaline 23031-32-5, Terbutaline sulfate 23214-92-8, Doxorubicin 23288-49-5, Probucol 23593-75-1, Clotrimazole 23869-24-1, O-(.beta.-Hydroxyethyl)-rutoside 24219-97-4, Mianserin 24390-14-5, Doxycycline hyclate 24729-96-2, Clindamycin phosphate 25046-79-1, Glisoxepide 25086-89-9, Vinyl acetate-N-vinylpyrrolidinone copolymer 25155-18-4, Methylbenzethonium chloride 25167-80-0, Chlorophenol 25301-02-4, Tyloxapol 25322-68-3 25332-39-2, Trazodone hydrochloride 25389-94-0, Kanamycin sulfate 25614-03-3, Bromocriptine 25655-41-8, **Povidone** iodine 25717-80-0, Molsidomine 25812-30-0, Gemfibrozil 25953-19-9, Cefazolin 26027-38-3, Nonoxynol 9 26171-23-3, Tolmetin 26652-09-5, Ritodrine 26675-46-7, Isoflurane 26787-78-0, Amoxicillin 26807-65-8, Indapamide 26839-75-8, Timolol 26944-48-9, Glibornuride 27203-92-5, Tramadol 27823-62-7, Chlortetracycline bisulfate 28088-64-4, Aminosalicylic acid 28395-03-1, Bumetanide 28657-80-9, Cinoxacin 28797-61-7, Pirenzepine 28860-95-9, Carbidopa 28911-01-5, Triazolam 28981-97-7, Alprazolam 29122-68-7, Atenolol 29679-58-1, Fenoprofen 30578-37-1, Amezinium metilsulfate 30685-43-9, Metildigoxin 31329-57-4, Naftidrofuryl 31431-39-7, Mebendazole 31637-97-5, Etofibrate 31828-71-4, Mexiletine 32672-69-8, Mesoridazine besylate 32780-64-6, Labetalol hydrochloride 32887-01-7, Amdinocillin 33005-95-7, Tiaprofenic acid 33286-22-5, Diltiazem hydrochloride 33402-03-8, Metaraminol bitartrate 33419-42-0 33996-33-7, Oxaceprol 34031-32-8, Auranofin 34183-22-7, Propafenone hydrochloride 34552-83-5, Loperamide hydrochloride 34580-13-7, Ketotifen

RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(embedding and encapsulation of controlled release particles)

IT 34787-01-4, Ticarcillin 36322-90-4, Piroxicam 36688-78-5 36791-04-5 37270-89-6, Heparin calcium 37517-28-5, Amikacin 37517-30-9, Acebutolol 38194-50-2, Sulindac 38260-01-4, Trientine hydrochloride 38304-91-5, Minoxidil 38363-40-5, Penbutolol 38396-39-3, Bupivacaine 38821-53-3, Cephradine 39562-70-4, Nitrendipine 40828-46-4, Suprofen 41859-67-0, Bezafibrate 42200-33-9, Nadolol 42399-41-7, Diltiazem 42540-40-9, Cefamandole nafate 49562-28-9, Fenofibrate 49745-95-1, Dobutamine hydrochloride 50370-12-2, Cefadroxil 50679-08-8, Terfenadine 50925-79-6, Colestipol 50972-17-3, Bacampicillin 51022-69-6, Amcinonide 51481-61-9, Cimetidine 51781-06-7, Carteolol 52468-60-7, Flunarizine 53164-05-9, Acemetacin 53179-11-6, Loperamide 53230-10-7, Mefloquine 53608-75-6, Pancrelipase 53994-73-3, Cefaclor 54063-53-5, Propafenone 54143-55-4, Flecainide 54182-58-0, Sucralfate 54965-21-8, Albendazole 54965-24-1, Tamoxifen citrate 55268-74-1, Praziquantel 55837-25-7, Buflomedil 55837-27-9, Piretanide 56392-17-7, Metoprolol tartrate 57109-90-7, Dipotassium chlorazepate 57432-61-8, Methylergonovine maleate 57435-86-6, Premazepam 58551-69-2, Carboprost tromethamine 59277-89-3, Acyclovir 59865-13-3, Cyclosporine 60166-93-0, Iopamidol 60200-06-8, Clorsulon 60833-22-9, Pyridoxal 5'-phosphate glutamate 61177-45-5, Clavulanate potassium 61489-71-2, Menotropin 61563-18-6, Soquinolol 62571-86-2, Captopril 62893-19-0, Cefoperazone 63527-52-6, Cefotaxime 63659-18-7, Betaxolol 64024-15-3, Pentazocine hydrochloride **64544-07-6**, **Cefuroxime axetil** 65277-42-1, Ketoconazole 65666-07-1, Silymarin 65899-73-2, Tioconazole 66108-95-0, Iohexol 66357-35-5, Ranitidine 66711-21-5, Apraclonidine 66734-13-2, Alclometasone dipropionate 68844-77-9, Astemizole 70458-96-7, Norfloxacin 72558-82-8, Ceftazidime 74978-16-8, Magaldrate 75330-75-5, Lovastatin 76095-16-4, Enalapril maleate 76420-72-9, Enalaprilat 76470-66-1, Loracarbef 76547-98-3, Lisinopril 76824-35-6, Famotidine 76963-41-2, Nizatidine 78110-38-0, Aztreonam 78266-06-5, Mebrofenin 79350-37-1, Cefixime 81103-11-9, Clarithromycin 83200-10-6, Anipamil 83905-01-5, Azithromycin 85721-33-1, Ciprofloxacin 92665-29-7, Cefprozil 102188-40-9, Acromycin 150977-36-9, Bromelain
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(embedding and encapsulation of controlled release particles)

IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, HIV; embedding and encapsulation of controlled release particles)

L52 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:535974 HCAPLUS
DN 127:166689
TI Enteric cellulosic microspheres for taste-masking of **cefuroxime axetil**: stability and in vitro release behavior
AU Cuna, M.; Lorenzo, M. L.; Vila-Jato, J. L.; Torres, D.; Alonso, M. J.
CS Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, 15706, Spain
SO Acta Technol. Legis Med. (**1996**), 7(3), 209-216
CODEN: ATLMEQ; ISSN: 1121-2098
PB Maccari
DT Journal
LA English
CC 63-6 (Pharmaceuticals)
AB **Cefuroxime axetil** (CA) was microencapsulated within various cellulosic polymers having a pH-dependent soly.: CAT, HPMCP-55 and HPMCP-50, with the final aim to mask its taste while assuring its release in the intestinal cavity. The drug release studies and the stability assay of the encapsulated mol., showed that the HPMCP-55 microspheres represent a useful approach to achieve the objectives proposed.

ST pharmaceutical microsphere cellulose taste masking cefuroxime
IT Dissolution rate
(enteric cellulosic microspheres for taste-masking of **cefuroxime axetil**)
IT Microspheres (drug delivery systems)
(enteric; enteric cellulosic microspheres for taste-masking of **cefuroxime axetil**)
IT **9050-31-1**, Hydroxypropyl methyl celluose phthalate 26266-58-0, Span 85 **52907-01-4**, Cellulose acetate trimellitate **64544-07-6, Cefuroxime axetil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enteric cellulosic microspheres for taste-masking of **cefuroxime axetil**)

L52 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:496696 HCAPLUS
DN 127:108801
TI Method of separating (R) and (S) isomers of 1-acetoxyethyl cefuroxime ester
IN Oszczapowicz, Irena; Gumiezna, Teresa; Olbrys, Leszek
PA Zaklady Produkcji Farmaceutycznej Bioton Bis Sp Z Oo, Pol.
SO Pol., 4 pp.
CODEN: POXXA7
DT Patent
LA Polish
IC ICM C07D501-34
CC 26-5 (Biomolecules and Their Synthetic Analogs)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PL 171244	B1	19970328	PL 1993-298836	19930506 <--

AB (R) and (S) isomers of the title compd., useful to treat infections caused by Gram-neg. and Gram-pos. bacteria (no data), were sepd. by dissolving the title compd. in EtOAc and/or Me2CO followed by decolorization with the active carbon (optional), addn. of EtOH or nPrOH or iPrOH, then addn. of H2O, filtration of solid (S)-isomer, and isolation of (R)-isomer from concd. mother liquor.
ST cefuroxime acetoxyethyl ester resoln
IT **64544-07-6P 64599-28-6P 64599-29-7P**
RL: PUR (Purification or recovery); PREP (Preparation)
(method of sepg. (R) and (S) isomers of 1-acetoxyethyl cefuroxime ester)
IT 64-17-5, Ethyl alcohol, uses 67-63-0, Isopropanol, uses **67-64-1**, **Acetone**, uses 71-23-8, n-Propanol, uses 141-78-6, Ethyl acetate, uses 7732-18-5, Water, uses
RL: NUU (Nonbiological use, unclassified); USES (Uses)
(solvent; method of sepg. (R) and (S) isomers of 1-acetoxyethyl cefuroxime ester)

L52 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:168614 HCAPLUS
DN 126:162299
TI Oral pharmaceutical composition containing antimicrobial actives and sustained release pantoprazole
IN Dietrich, Rango; Sachs, George; Ney, Hartmut; Benedikt, Gerald
PA Byk Gulden Lomberg Chemische Fabrik Gmbh, Germany
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-28
ICS A61K009-50
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 9702020 A1 19970123 WO 1996-EP2892 19960702 <--
W: AU, BG, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
US 5945124 A 19990831 US 1995-498386 19950705 <--
CA 2232450 AA 19970123 CA 1996-2232450 19960702 <--
AU 9665174 A1 19970205 AU 1996-65174 19960702 <--
EP 841903 A1 19980520 EP 1996-924849 19960702 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI
JP 11508577 T2 19990727 JP 1996-504811 19960702 <--
US 6068856 A 20000530 US 1998-42090 19980313 <--
PRAI US 1995-498386 19950705 <--
WO 1996-EP2892 19960702 <--

AB An oral pharmaceutical compn. of pantoprazole in pellet or tablet form wherein the pantoprazole is at least partly in slow-release form, is administered in combination with an antimicrobially-active ingredient for the treatment of disorders caused by Helicobacter. A tablet comprised (1) a core contg. pantoprazole Na.cntdot.3/2 H2O 45.1, Na2CO3 10, **mannitol** 20, HPMC 2910 (3 cps) 25, HPMC 2910 (15 cps) 4, and Ca **stearate** 2.1 mg, (2) a release-slowing layer contg. Et cellulose 9.85, micronized **lactose** 2.36, propylene glycol 0.98, and 25 % ammonia 0.8 mg, and (3) an enteric coating contg. Eudragit L 13.64 and tri-Et citrate 1.36 mg.

ST enteric coated tablet pantoprazole antimicrobial Helicobacter

IT Pellets (drug delivery systems)
Tablets (drug delivery systems)
(enteric-coated; oral compns. contg. antimicrobial actives and sustained-release pantoprazole)

IT Antimicrobial agents
Helicobacter
Stomach diseases
(oral compns. contg. antimicrobial actives and sustained-release pantoprazole)

IT 56-75-7, Chloramphenicol 57-62-5 57-92-1, Streptomycin, biological studies 59-87-0, Nitrofurazone 60-54-8, Tetracycline 61-33-6, Penicillin G, biological studies 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 69-53-4, Ampicillin 79-57-2, Oxytetracycline 87-08-1, Penicillin V 114-07-8, Erythromycin 153-61-7, Cephalothin 443-48-1, Metronidazole 564-25-0, Doxycycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 1405-87-4, Bacitracin 1406-11-7, Polymyxin 6506-37-2, Nimorazole 8063-07-8, Kanamycin 9002-89-5, Polyvinyl alcohol **9004-38-0**, Cellulose acetate phthalate **9004-57-3**, Ethyl cellulose **9050-31-1**, Hydroxypropyl **methyl cellulose** phthalate 10118-90-8, Minocycline 13292-46-1, Rifampicin 14882-18-9, Bismuth subsalicylate 15686-71-2, Cefalexin 18323-44-9, Clindamycin 19387-91-8, Tinidazole 25086-15-1, Methacrylic acidmethyl methacrylate copolymer 26787-78-0, Amoxicillin 28572-98-7, Ethyl methacrylate-Methacrylic acid copolymer 33434-24-1, Eudragit RS 35607-66-0, Cefoxitin **37205-99-5**, Carboxymethyl ethyl cellulose 37517-28-5, Amikacin 50370-12-2, Cefadroxil 51481-65-3, Mezlocillin **52907-01-4**, Cellulose acetate trimellitate 53994-73-3, Cefaclor 57644-54-9, Bismuth subcitrate 63527-52-6, Cefotaxime 64221-86-9, Imipenem **64544-07-6**, **Cefuroxime axetil** 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin **71138-97-1**, Hydroxypropyl **methyl cellulose** acetate succinate 76470-66-1, Loracarbef 81103-11-9, Clarithromycin 82419-36-1, Ofloxacin 83905-01-5, Azithromycin 85721-33-1, Ciprofloxacin 87239-81-4, Cefpodoxime proxetil 87726-17-8, Panipenem 96036-03-2, Meropenem 102625-70-7, Pantoprazole 138786-67-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. contg. antimicrobial actives and sustained-release pantoprazole)

L52 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:165311 HCAPLUS

DN 126:162298
TI Oral pharmaceutical compositions with delayed release of reversible proton pump inhibitors
IN Dietrich, Rango; Sachs, George; Postius, Stefan; Ney, Hartmut; Senn-Bilfinger, Joerg
PA Byk Gulden Lomberg Chemische Fabrik Gmbh, Germany
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-28
ICS A61K009-50
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9702021	A1	19970123	WO 1996-EP2893	19960702 <--
	W: AU, BG, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6132768	A	20001017	US 1995-498391	19950705 <--
	CA 2225628	AA	19970123	CA 1996-2225628	19960702 <--
	AU 9665175	A1	19970205	AU 1996-65175	19960702 <--
	AU 711577	B2	19991014		
	EP 841904	A1	19980520	EP 1996-924850	19960702 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
	JP 11508578	T2	19990727	JP 1996-504812	19960702 <--
PRAI	US 1995-498391	19950705 <--			
	WO 1996-EP2893	19960702 <--			

AB An oral pharmaceutical compn. of a reversible proton pump inhibitor in pellet or tablet form is disclosed. The reversible proton pump inhibitor is at least partly in slow-release form and administered in combination with an antimicrobially-active ingredient in a single dosage unit or in sep. dosage units in a single package, for the treatment of disorders caused by Helicobacter. A tablet comprised a core contg. 8-(2-methoxycarbonylamino-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine 119.8, Na carboxymethyl starch 21, microcryst. cellulose 21, starch 19.4, and Mg **stearate** 5 mg and a release-slowing layer contg. Et cellulose 9.85, micronized **lactose** 2.37, and propylene glycol 0.98 mg.

ST Helicobacter ulcer imidazopyridine deriv bactericide tablet
IT Antiulcer agents
Helicobacter pylori
Pellets (drug delivery systems)
Tablets (drug delivery systems)
(oral compns. with delayed release of reversible proton pump inhibitors and antimicrobial agents)
IT 56-75-7, Chloramphenicol 57-62-5 57-92-1, Streptomycin, biological studies 59-87-0, Nitrofurazone 60-54-8, Tetracycline 61-33-6, Penicillin G, biological studies 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 69-53-4, Ampicillin 79-57-2, Oxytetracycline 87-08-1, Penicillin V 114-07-8, Erythromycin 153-61-7, Cephalothin 443-48-1, Metronidazole 564-25-0, Doxycycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 1405-87-4, Bacitracin 1406-11-7, Polymyxin 6506-37-2, Nimorazole 8063-07-8, Kanamycin 10118-90-8, Minocycline 13292-46-1, Rifampicin 14882-18-9, Bismuth subsalicylate 15686-71-2, Cefalexin 18323-44-9, Clindamycin 19387-91-8, Tinidazole 26787-78-0, Amoxicillin 35607-66-0, Cefoxitin 37517-28-5, Amikacin 50370-12-2, Cefadroxil 51481-65-3, Mezlocillin 53994-73-3, Cefaclor 57644-54-9, Bismuth subcitrate 63527-52-6, Cefotaxime 64221-86-9, Imipenem **64544-07-6, Cefuroxime axetil** 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 76081-98-6 76470-66-1, Loracarbef 79707-34-9 81103-11-9, Clarithromycin 82419-36-1, Ofloxacin 83905-01-5, Azithromycin 85721-33-1, Ciprofloxacin 87239-81-4, Cefpodoxime proxetil 87726-17-8, Panipenem 96036-03-2, Meropenem

96428-79-4 115607-61-9 125500-29-0 158364-57-9 158364-58-0
158364-59-1 158364-63-7 158364-64-8 158364-65-9 158364-66-0
158364-67-1 158364-68-2 158364-69-3 158364-70-6 169319-20-4
169319-21-5 169319-22-6 169319-24-8
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. with delayed release of reversible proton pump inhibitors and antimicrobial agents)

L52 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:152831 HCAPLUS
DN 126:242737
TI pH-dependent cellulosic microspheres containing **cefuroxime axetil**: stability and in vitro release behavior
AU Cuna, M.; Lorenzo-Lamosa, M. L.; Vila-Jato, J. L.; Torres, D.; Alonso, M. J.
CS Faculty Pharmacy, University Santiago de Compostela, Santiago de Compostela, Spain
SO Drug Dev. Ind. Pharm. (**1997**), 23(3), 259-265
CODEN: DDIPD8; ISSN: 0363-9045
PB Dekker
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
AB **Cefuroxime axetil** (CA) was encapsulated in pH-dependent cellulose microspheres with the final aim of masking taste while assuring its release into the intestinal cavity. The polymers selected were: CAT (cellulose acetate trimellitate) and 2 types of hydroxypropyl **Me cellulose** phthalate, HPMCP-55 and HPMCP-50. The CA-loaded CAT and HPMCP-55 microspheres were obtained by a solvent extn. procedure, whereas the encapsulation of CA into HPMCP-50 microspheres was only achieved by a solvent evapn. technique. All the formulations displayed pH-dependent release profiles, releasing their total content in 30 min when exposed to an aq. medium of pH 6.0. Anal. of the encapsulated mol. by HPLC revealed that a problem of compatibility arises between CA and CAT, leading to the formulation of a high amt. of CA impurities. By contrast, a min. amt. of impurities was detected upon encapsulation of CA within JPMCP, this amt. being lower for HPMCP-55 than for HPMPC-50. Finally, the taste-masking test carried out for the formulation made of HPMCP-55 evidenced the efficacy of the polymer coating in preventing the release of CA in an acidic medium and thus masking its taste.
ST cellulose microsphere **cefuroxime axetil** stability release
IT Bitterness
Dissolution rate
Microencapsulation
Microspheres (drug delivery systems)
Particle size distribution
Physicochemical drug interactions
(stability of and drug release from pH-dependent cellulose microspheres contg. **cefuroxime axetil**)
IT **64544-07-6, Cefuroxime axetil**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stability of and drug release from pH-dependent cellulose microspheres contg. **cefuroxime axetil**)
IT **9050-31-1**, Hydroxypropyl **methyl cellulose** phthalate **52907-01-4**, Cellulose acetate trimellitate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stability of and drug release from pH-dependent cellulose microspheres contg. **cefuroxime axetil**)

L52 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1987:428397 HCAPLUS
DN 107:28397

TI Cefuroxim axetil tablets
IN Anwar, Jamshed; Deutsch, David Samuel
PA Glaxo Group Ltd., UK
SO Ger. Offen., 9 pp.
CODEN: GWXXBX
DT Patent
LA German
IC ICM A61K031-545
ICS A61K009-32; A61J003-10
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3633292	A1	19870409	DE 1986-3633292	19860930 <--
	ZA 8607318	A	19870527	ZA 1986-7318	19860925 <--
	IL 80165	A1	19910610	IL 1986-80165	19860926 <--
	DK 8604624	A	19870331	DK 1986-4624	19860929 <--
	SE 8604114	A	19870331	SE 1986-4114	19860929 <--
	NO 8603863	A	19870331	NO 1986-3863	19860929 <--
	NO 173636	B	19931004		
	NO 173636	C	19940112		
	AU 8663232	A1	19870402	AU 1986-63232	19860929 <--
	AU 594082	B2	19900301		
	GB 2181052	A1	19870415	GB 1986-23340	19860929 <--
	GB 2181052	B2	19891018		
	EP 223365	A2	19870527	EP 1986-307459	19860929 <--
	EP 223365	A3	19880608		
	EP 223365	B1	19910227		
	R: DE, NL, SE				
	FR 2591597	A1	19870619	FR 1986-13539	19860929 <--
	FR 2591597	B1	19890602		
	ES 2002382	A6	19880801	ES 1986-2263	19860929 <--
	CH 672736	A	19891229	CH 1986-3900	19860929 <--
	CA 1282331	A1	19910402	CA 1986-519257	19860929 <--
	BE 905518	A1	19870330	BE 1986-217227	19860930 <--
	NL 8602466	A	19870416	NL 1986-2466	19860930 <--
	JP 62123118	A2	19870604	JP 1986-230233	19860930 <--
	AT 8602609	A	19910115	AT 1986-2609	19860930 <--
	AT 393081	B	19910812		
	US 4897270	A	19900130	US 1988-291364	19881230 <--
PRAI	GB 1985-24001		19850930 <--		
	US 1986-913267		19860930 <--		
	US 1987-71163		19870708 <--		

AB **Cefuroxime axetil** (I) tablets are coated to mask the bitter taste of I. The low bioavailability of these tablets is eliminated by using an enterosol. coat and by ensuring dissoln. of the tablet core immediately after dissoln. of the coat. Tablet cores are made of I (125 mg cerufoxime equiv.), microcryst. cellulose 47.51, **Na croscarmellose** type A 20.00, Na lauryl sulfate 2.25, SiO2 0.63, and hydrogenated vegetable oil 4.25 mg. The film coat contained **hydroxypropylcellulose** 10, propylene glycol 0.60, Me hydroxybenzoate 0.10, Opastray White M-1-7120 0.08, Pr hydroxybenzoate 0.08 and water to 100% by wt. The av. dissoln. time of the coat was 4.9 s.

ST **cefuroxime axetil** coated tablet
IT **9004-32-4**, Carboxymethylcellulose **9004-65-3**, Hydroxypropylmethylcellulose
RL: BIOL (Biological study)
(**cefuroxime axetil** tablets contg.)
IT **64544-07-6, Cefuroxime axetil**
RL: BIOL (Biological study)
(tablet)

L52 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1984:478882 HCAPLUS
Correction of: 1984:197791

DN 101:78882
Correction of: 100:197791
TI Amorphous **cefuroxime axetil** for improved bioavailability from the gastrointestinal tract.
IN Crisp, Harold Alfred; Clayton, John Charles; Elliott, Leonard Godfrey; Wilson, Edward McKenzie
PA Glaxo Group Ltd., UK
SO Ger. Offen., 36 pp.
CODEN: GWXXBX
DT Patent
LA German
IC C07D501-34; A61K031-54; A61K031-325; A61K031-19; A61K031-34
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 26
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	DE 3327449	A1	19840202	DE 1983-3327449	19830729	<--
	BE 897422	A1	19840130	BE 1983-211274	19830729	<--
	SE 8304208	A	19840131	SE 1983-4208	19830729	<--
	SE 453195	B	19880118			
	SE 453195	C	19880428			
	FI 8302757	A	19840131	FI 1983-2757	19830729	<--
	FI 76093	B	19880531			
	FI 76093	C	19880909			
	DK 8303490	A	19840131	DK 1983-3490	19830729	<--
	DK 164507	B	19920706			
	DK 164507	C	19921123			
	NO 8302773	A	19840131	NO 1983-2773	19830729	<--
	NO 163897	B	19900430			
	NO 163897	C	19900808			
	AU 8317417	A1	19840202	AU 1983-17417	19830729	<--
	AU 566881	B2	19871105			
	FR 2531087	A1	19840203	FR 1983-12561	19830729	<--
	FR 2531087	B1	19851122			
	NL 8302705	A	19840216	NL 1983-2705	19830729	<--
	JP 59044391	A2	19840312	JP 1983-137871	19830729	<--
	JP 07030084	B4	19950405			
	GB 2127401	A1	19840411	GB 1983-20518	19830729	<--
	GB 2127401	B2	19860416			
	HU 31230	O	19840428	HU 1983-2715	19830729	<--
	HU 190603	B	19860929			
	EP 107276	A2	19840502	EP 1983-304405	19830729	<--
	EP 107276	A3	19850306			
	EP 107276	B1	19871007			
	R: DE, NL, SE					
	ZA 8305579	A	19840926	ZA 1983-5579	19830729	<--
	ES 524590	A1	19850601	ES 1983-524590	19830729	<--
	US 4562181	A	19851231	US 1983-518693	19830729	<--
	AT 8302767	A	19860615	AT 1983-2767	19830729	<--
	AT 382154	B	19870126			
	CH 657134	A	19860815	CH 1983-4180	19830729	<--
	SU 1266471	A3	19861023	SU 1983-3624504	19830729	<--
	IL 69375	A1	19861231	IL 1983-69375	19830729	<--
	CA 1240313	A1	19880809	CA 1983-433554	19830729	<--
	CS 259515	B2	19881014	CS 1983-5687	19830729	<--
	PL 156001	B1	19920131	PL 1983-243228	19830729	<--
	US 4820833	A	19890411	US 1986-938140	19861204	<--
	US 4994567	A	19910219	US 1988-258886	19881018	<--
	US 5013833	A	19910507	US 1988-258908	19881018	<--
	SK 277896	B6	19950711	SK 1991-4031	19911223	<--
	CZ 280528	B6	19960214	CZ 1991-4031	19911223	<--
	DK 9200683	A	19920525	DK 1992-683	19920525	<--
PRAI	GB 1982-22019	19820730	<--			
	US 1983-518671	19830729	<--			
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US 1985-781505 19850930 <--
US 1986-938140 19861204 <--

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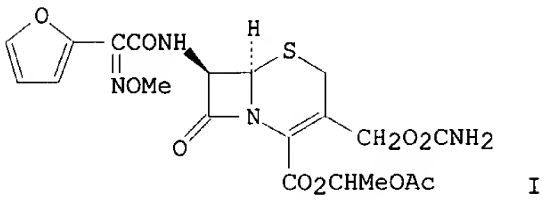


I

AB A highly pure amorphous mixt. (1:1) of R- [**64599-28-6**] and S- **cefuroxime axetil** (I) [**64599-29-7**] was prepd. by spray-, freeze-, or roller-drying of or pptn. from a soln. of org. solvent or solvent-H2O mixts. Highly pure Na cefuroxime [56238-63-2] is prepd. by the reaction of (6R,7R)-3-hydroxymethyl-7-[(Z)-2-(2-furyl)-2-methoxyiminoacetamido]ceph-3-em-4-carboxylic acid [56271-94-4] chlorosulfonyl isocyanate [1189-71-5] in MeOAc [79-20-9] at -5 to -15.degree., hydrolysis by addn. of H2O at 18.degree., and crystn. by the addn. of Na 2-ethylhexanoate in Me2CO [**67-64-1**] or MeOAc. The cefuroxime Na salt was esterified with (RS)-1-acetoxyethyl bromide [70091-16-6] in dimethylacetamide at 1.degree.. The impurity content was 1.8% and the isomer ratio was 1.09:1 as detd. byn HPLC. A 10% soln. of the product in Me2CO was spray-dried with air at inlet and outlet temps. of 124 and 70.degree., resp. The hollow beads obtained had 2% impurities, 0.15% solvent, and 0.8% H2O; the isomer ratio was 1.04:1 and the product was amorphous. Formulation of tablets, capsules, powders for oral suspensions, and oily suspensions contg. 250-300 mg of I is described.

ST **cefuroxime axetil** pharmaceutical; spray drying

cefuroxime axetil

IT Drying
Freeze drying
Solvents
Ligroine
RL: PREP (Preparation)
(in prepn. of amorphous **cefuroxime axetil**, for pharmaceuticals)

IT Drying
(spray, in prepn. of amorphous **cefuroxime axetil**, for pharmaceuticals)

IT 70091-16-6
RL: RCT (Reactant)
(esterification by, of cefuroxime)

IT 64-17-5, uses and miscellaneous 67-56-1, uses and miscellaneous **67-64-1**, uses and miscellaneous 67-66-3, uses and miscellaneous 75-05-8, uses and miscellaneous 75-09-2, uses and miscellaneous 79-20-9 108-20-3 109-99-9, uses and miscellaneous 123-91-1, uses and miscellaneous 141-78-6, uses and miscellaneous
RL: BIOL (Biological study)
(in prepn. of amorphous **cefuroxime axetil**, for pharmaceuticals)

IT 56238-63-2P
RL: PREP (Preparation)
(prepn. and esterification with acetoxyethyl bromide)

IT **64544-07-6P**
RL: PREP (Preparation)
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)

IT **64599-29-7P**

RL: PREP (Preparation)
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)

IT **64599-28-6P**
RL: PREP (Preparation)
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)

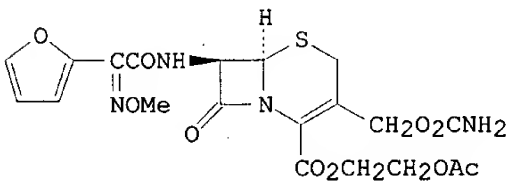
IT 56271-94-4
RL: RCT (Reactant)
(reaction of, of chlorosulfonyl isocyanate)

IT 1189-71-5
RL: RCT (Reactant)
(reaction of, with hydroxymethylcephemcarboxylic acid)

L52 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2001 ACS
AN 1984:197791 HCAPLUS
DN 100:197791
TI Amorphous **cefuroxime axetil** for improved bioavailability from the gastrointestinal tract.
IN Crisp, Harold Alfred; Clayton, John Charles; Elliott, Leonard Godfrey; Wilson, Edward McKenzie
PA Glaxo Group Ltd., UK
SO Ger. Offen., 36 pp.
CODEN: GWXXBX
DT Patent
LA German
IC C07D501-34; A61K031-54; A61K031-325; A61K031-19; A61K031-34
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 26

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 3327449 A1		**19840202**	DE 1983-3327449	19830729
PRAI GB 1982-22019		19820730		

GI



I

AB A highly pure amorphous mixt. (.apprx.1:1) of R- [**67-64-1**] and S-**cefuroxime axetil** (I) [**64599-29-7**] was prepd. by spray-, freeze-, or roller-drying of or pptn. from a soln. of org. solvent or solvent-H2O mixts. Highly pure Na cefuroxime [56238-63-2] is prepd. by the reaction of (6R,7R)-3-hydroxymethyl-7-[(Z)-2-(2-furyl)-2-methoxyiminoacetamido]ceph-3-em-4-carboxylic acid [56271-94-4] with chlorosulfonyl isocyanate [1189-71-5] in MeOAc [79-20-9] at -5 to -15.degree., hydrolysis by addn. of H2O at 18.degree., and crystn. by the addn. of Na 2-ethylhexanoate in Me2CO [**67-64-1**] or MeOAc. The cefuroxime Na was esterified with (RS)-1-acetoxyethyl bromide [70091-16-6] in dimethylacetamide at 1.degree.. By high-performance liq. chromatog., the impurity content was 1.8% and the isomer ratio was 1.09:1. A 10% soln. of the product in Me2CO was spray-dried with air at inlet and outlet temps. of 124 and 70.degree., resp. The hollow beads obtained had 2% impurities, 0.15% solvent, and 0.8% H2O; the isomer ratio was 1.04:1 and the product was amorphous. Formulation of tablets, capsules, powders for oral suspensions, and oily suspensions contg. 250-300 mg of I is described.

ST **cefuroxime axetil** amorphous prepn; acetoxyethyl cefuroxime amorphous prepn; spray drying **cefuroxime axetil**

IT Drying
Freeze drying
Solvents
Ligroine
RL: PREP (Preparation)
(in **cefuroxime axetil** amorphous form prepn., for pharmaceuticals)

IT Drying
(spray, in **cefuroxime axetil** amorphous form prepn., for pharmaceuticals)

IT 70091-16-6
RL: RCT (Reactant)
(esterification by, of cefuroxime)

IT 64-17-5, uses and miscellaneous 67-56-1, uses and miscellaneous **67-64-1**, uses and miscellaneous 67-66-3, uses and miscellaneous 75-05-8, uses and miscellaneous 75-09-2, uses and miscellaneous 79-20-9 108-20-3 109-99-9, uses and miscellaneous 123-91-1, uses and miscellaneous 141-78-6, uses and miscellaneous
RL: BIOL (Biological study)
(in **cefuroxime axetil** amorphous form prepn., for pharmaceuticals)

IT 56238-63-2P
RL: PREP (Preparation)
(prepn. and esterification with acetoxyethyl bromide)

IT **64544-07-6P**
RL: PREP (Preparation)
(prepn. of amorphous mixts. of, for bioavailability enhancement)

IT **64599-29-7P**
RL: PREP (Preparation)
(prepn. of amorphous mixts. with R-isomer, for bioavailability enhancement)

IT **64599-28-6P**
RL: PREP (Preparation)
(prepn. of amorphous mixts. with S-isomer, for bioavailability enhancement)

IT 56271-94-4
RL: RCT (Reactant)
(reaction of, with chlorosulfonyl isocyanate)

IT 1189-71-5
RL: RCT (Reactant)
(reaction of, with hydroxymethylcephem carboxylic acid)

=> sel hit rn 152

E11 THROUGH E35 ASSIGNED

=> fil reg

FILE 'REGISTRY' ENTERED AT 08:00:21 ON 30 MAR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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STRUCTURE FILE UPDATES: 29 MAR 2001 HIGHEST RN 329346-67-0
DICTIONARY FILE UPDATES: 29 MAR 2001 HIGHEST RN 329346-67-0

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT

for details.

=> d his l53-

(FILE 'HCAPLUS' ENTERED AT 07:58:20 ON 30 MAR 2001)

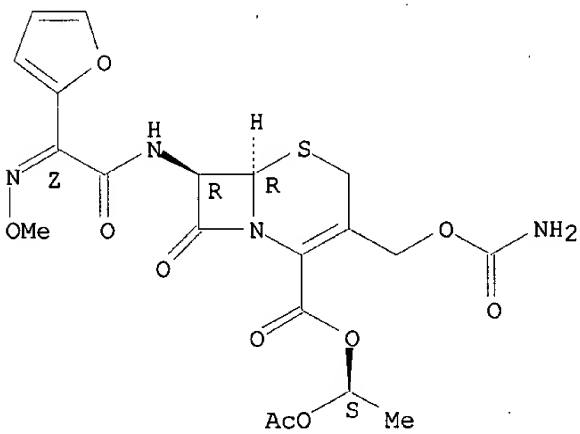
FILE 'HCAPLUS' ENTERED AT 07:59:56 ON 30 MAR 2001
SEL HIT RN L52

FILE 'REGISTRY' ENTERED AT 08:00:21 ON 30 MAR 2001
L53 25 S E11-E35
L54 3 S L53 AND L8
L55 22 S L53 NOT L54

=> d ide can tot l54

L54 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2001 ACS
RN **64599-29-7** REGISTRY
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1S)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, [6R-[2(S*),6.alpha.,7.beta.(Z)]]-
FS STEREOSEARCH
MF **C20 H22 N4 O10 S**
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



18 REFERENCES IN FILE CA (1967 TO DATE)
18 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:237767

REFERENCE 2: 132:40509

REFERENCE 3: 131:82563

REFERENCE 4: 131:78440

REFERENCE 5: 129:265323

REFERENCE 6: 129:189164

REFERENCE 7: 127:108801

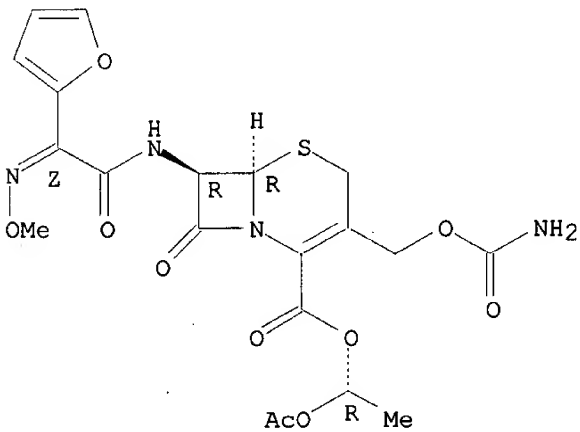
REFERENCE 8: 124:306523

REFERENCE 9: 120:173205

REFERENCE 10: 116:247887

L54 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2001 ACS
RN **64599-28-6** REGISTRY
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1R)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, [6R-[2(R*),6.alpha.,7.beta.(Z)]]-
FS STEREOSEARCH
MF **C20 H22 N4 O10 S**
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



18 REFERENCES IN FILE CA (1967 TO DATE)
18 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:237767

REFERENCE 2: 132:40509

REFERENCE 3: 131:82563

REFERENCE 4: 129:265323

REFERENCE 5: 129:189164

REFERENCE 6: 127:108801

REFERENCE 7: 124:306523

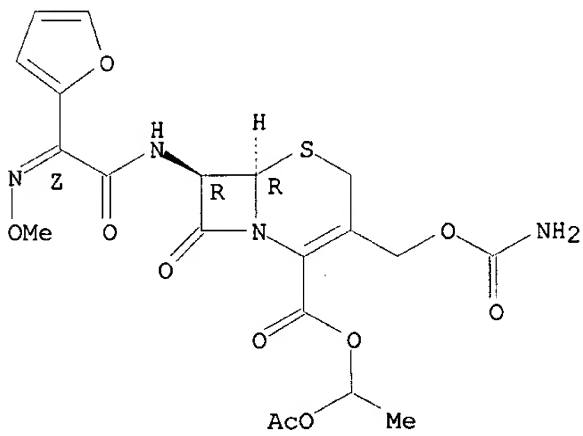
REFERENCE 8: 120:173205

REFERENCE 9: 116:247887

REFERENCE 10: 116:151434

L54 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2001 ACS
RN **64544-07-6** REGISTRY
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, [6R-[6.alpha.,7.beta.(Z)]]-
OTHER NAMES:
CN Ceftin
CN Cefuroxime 1-acetoxyethyl ester
CN **Cefuroxime axetil**
CN Elobact
FS STEREOSEARCH
MF **C20 H22 N4 O10 S**
CI COM
LC STN Files: AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IMSDIRECTORY, IPA, MEDLINE, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



241 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
241 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212813

REFERENCE 2: 134:202440

REFERENCE 3: 134:198075

REFERENCE 4: 134:183492

REFERENCE 5: 134:61542

REFERENCE 6: 134:61525

REFERENCE 7: 133:331979

REFERENCE 8: 133:291106

REFERENCE 9: 133:256835

REFERENCE 10: 133:256626

=> d ide can tot 155

L55 ANSWER 1 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **74811-65-7** REGISTRY
CN Croscarmellose sodium (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AcDiSol
CN Primellose
CN Sodium Croscarmellose
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration
LC STN Files: BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CHEMLIST, CIN, CSCHEM, EMBASE, IPA, MRCK*, MSDS-OHS, PROMT, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
461 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
463 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:198103

REFERENCE 2: 134:183499

REFERENCE 3: 134:180342

REFERENCE 4: 134:168378

REFERENCE 5: 134:152663

REFERENCE 6: 134:152653

REFERENCE 7: 134:91168

REFERENCE 8: 134:91155

REFERENCE 9: 134:91152

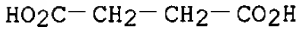
REFERENCE 10: 134:76385

L55 ANSWER 2 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **71138-97-1** REGISTRY
CN Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxypropyl methyl cellulose acetate succinate
CN Aqoat
CN Aqoat AS-HF
CN Aqoat AS-L
CN Aqoat AS-LF
CN Aqoat AS-MF

CN AS-HG
CN AS-LG
CN AS-MF
CN HPMCAS
CN Hydroxypropyl methyl cellulose acetate succinate
CN SA-M
CN SA-M (polysaccharide)
DR 154608-47-6
MF C4 H6 O4 . x C3 H8 O2 . x C2 H4 O2 . x C H4 O . x Unspecified
LC STN Files: BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, EMBASE, IPA, MEDLINE, TOXLINE, TOXLIT, USPATFULL

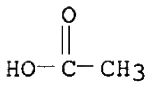
CM 1

CRN 110-15-6
CMF C4 H6 O4



CM 2

CRN 64-19-7
CMF C2 H4 O2



CM 3

CRN 9004-65-3
CMF C3 H8 O2 . x C H4 O . x Unspecified

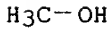
CM 4

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

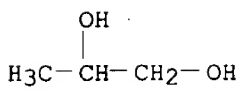
CM 5

CRN 67-56-1
CMF C H4 O



CM 6

CRN 57-55-6
CMF C3 H8 O2



279 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
279 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212738

REFERENCE 2: 134:212735

REFERENCE 3: 134:212734

REFERENCE 4: 134:212627

REFERENCE 5: 134:212617

REFERENCE 6: 134:198085

REFERENCE 7: 134:183483

REFERENCE 8: 134:152676

REFERENCE 9: 134:105888

REFERENCE 10: 134:61541

L55 ANSWER 3 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **52907-01-4** REGISTRY
CN Cellulose, acetate 1,2,4-benzenetricarboxylate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Cellulose acetate trimellitate
CN Cellulose acetotrimellitate
MF C9 H6 O6 . x C2 H4 O2 . x Unspecified
PCT Manual registration
LC STN Files: BIOBUSINESS, BIOSIS, CA, CAPLUS, CHEMCATS, CHEMLIST, CIN, CSCHEM, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PROMT, TOXLINE, TOXLIT, USPATFULL
Other Sources: TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

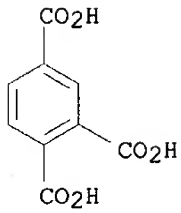
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

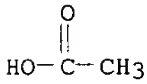
CM 2

CRN 528-44-9
CMF C9 H6 O6



CM 3

CRN 64-19-7
CMF C2 H4 O2



124 REFERENCES IN FILE CA (1967 TO DATE)
124 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212735

REFERENCE 2: 134:198075

REFERENCE 3: 134:197977

REFERENCE 4: 134:88333

REFERENCE 5: 134:61541

REFERENCE 6: 134:32965

REFERENCE 7: 133:315645

REFERENCE 8: 133:271683

REFERENCE 9: 133:198677

REFERENCE 10: 133:182970

L55 ANSWER 4 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **37205-99-5** REGISTRY
CN Cellulose, carboxymethyl ethyl ether (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Carboxymethyl ethyl cellulose
CN Ethyl carboxymethyl cellulose
MF C2 H6 O . x C2 H4 O3 . x Unspecified
PCT Manual registration
LC STN Files: BIOBUSINESS, BIOSIS, CA, CAPLUS, CHEMLIST, IFICDB, IFIPAT, IFIUDB, IPA, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

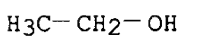
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 79-14-1
CMF C2 H4 O3

CM 3

CRN 64-17-5
CMF C2 H6 O



211 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
211 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:209034

REFERENCE 2: 134:198085

REFERENCE 3: 134:58755

REFERENCE 4: 134:9360

REFERENCE 5: 133:352264

REFERENCE 6: 133:282704

REFERENCE 7: 133:168404

REFERENCE 8: 133:168369

REFERENCE 9: 133:155429

REFERENCE 10: 133:140071

L55 ANSWER 5 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9063-38-1** REGISTRY
CN Starch, carboxymethyl ether, sodium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Carboxymethyl starch sodium salt
CN Deprogel
CN Emsize CMS 100
CN Emsize CMS 60
CN Estarl A 100
CN Explotab
CN F 500 Papeal No. 50
CN Kiprogum F 500
CN Papeal F 500 No. 50
CN Polvitex Z
CN Polytex 60
CN Primojel
CN Sodium carboxymethyl starch
CN Sodium CM-starch
CN Sodium starch glycolate

CN Solvitose CL
CN Vivastar P 5000
DR 9061-71-6, 60351-56-6, 65931-51-3
MF C2 H4 O3 . x Na . x Unspecified
CI COM
PCT Manual registration
LC STN Files: BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MSDS-OHS, PROMT, TOXLINE, TOXLIT, USPATFULL
Other Sources: DSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

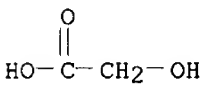
CM 1

CRN 9005-25-8
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 79-14-1
CMF C2 H4 O3



726 REFERENCES IN FILE CA (1967 TO DATE)
18 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
727 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212690

REFERENCE 2: 134:198085

REFERENCE 3: 134:198079

REFERENCE 4: 134:183500

REFERENCE 5: 134:180217

REFERENCE 6: 134:168379

REFERENCE 7: 134:152554

REFERENCE 8: 134:136699

REFERENCE 9: 134:120972

REFERENCE 10: 134:83627

L55 ANSWER 6 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9050-31-1** REGISTRY
CN Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxypropyl methyl cellulose phthalate
CN Cellulose phthalate hydroxypropyl methyl ether
CN HP 5
CN HP 5 (cellulose derivative)
CN HP 50
CN HP 50 (cellulose derivative)

CN HP 50F
CN HP 55
CN HP 55F
CN HP 55UF
CN HPMCP
CN HPMCP 55
CN HPMCP HP 55S
CN Hydroxpropyl methyl cellulose phthalate
CN Hydroxypropyl methyl cellulose phthalate
CN Hydroxypropyl methylcelluose phthalate
CN Hydroxypropylmethylcellulose hydrogen phthalate
DR 9087-42-7, 168395-88-8, 37324-31-5, 42612-68-0, 52624-22-3
MF C8 H6 O4 . x C3 H8 O2 . x C H4 O . x Unspecified
CI COM
PCT Manual registration
LC STN Files: BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

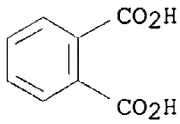
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

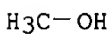
CM 2

CRN 88-99-3
CMF C8 H6 O4



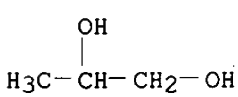
CM 3

CRN 67-56-1
CMF C H4 O



CM 4

CRN 57-55-6
CMF C3 H8 O2



828 REFERENCES IN FILE CA (1967 TO DATE)

5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
829 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212735

REFERENCE 2: 134:198085

REFERENCE 3: 134:198075

REFERENCE 4: 134:197977

REFERENCE 5: 134:183483

REFERENCE 6: 134:152676

REFERENCE 7: 134:152663

REFERENCE 8: 134:120953

REFERENCE 9: 134:105888

REFERENCE 10: 134:93397

L55 ANSWER 7 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9032-42-2** REGISTRY
CN Cellulose, 2-hydroxyethyl methyl ether (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxyethyl methyl cellulose
CN Benecel ME 233P
CN Cesca MHEC 6000PR
CN Culminal MHEC
CN Culminal MHEC 15000PFF
CN Culminal MHEC 300000PR
CN Culminal MHEC 40000P
CN Hi-Metolose SEB 60TG
CN Hydroxyethyl methyl cellulose
CN Hymetellose
CN Methyl hydroxyethyl cellulose
CN Metolose SE
CN Metolose SEB 02T
CN Metolose SEB 04T
CN Metolose SEB 15000
CN Metolose SEB 15T
CN Metolose SEB 30000
CN Metolose SEB 30T
CN Metolose SEB 4000
CN Metolose SEW 30T
CN Metolose SEW 4000
CN MH 4000
CN Modocoll E 100
CN Modocoll E 20
CN OMC 181
CN OMC 853B
CN SEW 04T
CN SHV-WF
CN SNB
CN SNB (binder)
CN SNB 100T
CN Tylopur MH
CN Tylopur MH 300
CN Tylose 4000
CN Tylose MG 50
CN Tylose MH
CN Tylose MH 1000
CN Tylose MH 10000
CN Tylose MH 10000K

CN Tylose MH 1000P
CN Tylose MH 20
CN Tylose MH 2000
CN Tylose MH 2000P
CN Tylose MH 2000XP
CN Tylose MH 200K
CN Tylose MH 200KG4
CN Tylose MH 200XP
CN Tylose MH 200YP2
CN Tylose MH 300
CN Tylose MH 300P
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 51990-47-7
MF C2 H6 O2 . x C H4 O . x Unspecified
CI COM
PCT Manual registration
LC STN Files: ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CHEMLIST, CSCHEM, DETHERM*, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PIRA, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 107-21-1
CMF C2 H6 O2

HO—CH_2—CH_2—OH

CM 3

CRN 67-56-1
CMF C H4 O

H_3C—OH

755 REFERENCES IN FILE CA (1967 TO DATE)
32 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
756 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:209717

REFERENCE 2: 134:209535

REFERENCE 3: 134:197893

REFERENCE 4: 134:182364

REFERENCE 5: 134:164430

REFERENCE 6: 134:108055

REFERENCE 7: 134:103322

REFERENCE 8: 134:76387

REFERENCE 9: 134:75587

REFERENCE 10: 134:73170

L55 ANSWER 8 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-70-0** REGISTRY
CN Cellulose, nitrate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3/1S
CN A 280
CN A 300A
CN A 5020
CN A 5021
CN A 5021 (cellulose derivative)
CN A 5023
CN AH 27
CN BA 85
CN Bergerac NC
CN Biotrace NT
CN BK2-W
CN BK2-Z
CN C 1145
CN C 2018
CN CA 80
CN CA 80-15
CN CA 85
CN Celline 200
CN Celline FM 200
CN Celline FM 200S
CN Celloidin
CN Celnova BTH 1/2
CN Celva
CN CN 80
CN CN 80 (cellulose derivative)
CN CN 85
CN CN 88
CN Collodion
CN Collodion cotton
CN Collodion wool
CN Colloxylin
CN Colloxylin VNV
CN Corial EM Finish F
CN Corial EM Finish LS
CN Daicel FQRS 1/2
CN Daicel H 7
CN Daicel RA 1/16
CN Daicel RS
CN Daicel RS 1
CN Daicel RS 1/16
CN Daicel RS 1/2
CN Daicel RS 1/2H
CN Daicel RS 20
CN Daicel RS 200
CN Daicel RS 7
CN Daicel SS
CN Daicel SS 1/2
CN Daicel SS 1/2a
CN Daicel SS 1/2b
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 8050-69-9, 8050-70-2, 1339-76-0, 124362-83-0, 60649-57-2, 37228-31-2,

37317-48-9, 72026-64-3, 72026-68-7, 152264-12-5, 88386-25-8, 188626-79-1,
246848-29-3
MF H N O3 . x Unspecified
CI COM
PCT Manual registration, Polyother, Polyother only
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT,
APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS,
CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,
DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE,
MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, TOXLINE,
TOXLIT, TULSA, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

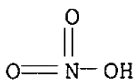
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 7697-37-2
CMF H N O3



9102 REFERENCES IN FILE CA (1967 TO DATE)
144 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9110 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:216320

REFERENCE 2: 134:212431

REFERENCE 3: 134:210172

REFERENCE 4: 134:210149

REFERENCE 5: 134:209534

REFERENCE 6: 134:208483

REFERENCE 7: 134:204755

REFERENCE 8: 134:200579

REFERENCE 9: 134:200577

REFERENCE 10: 134:200576

L55 ANSWER 9 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-67-5** REGISTRY
CN Cellulose, methyl ether (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Adulsin
CN Avicel SG
CN Bagolax
CN Benecel M 02

CN Benecel MC 4000PS
CN Benecel MO 42
CN Bufapto Methalose
CN Bulkaloid
CN Celacol M
CN Celacol M 20
CN Celacol M 20P
CN Celacol M 2500
CN Celacol M 450
CN Celacol MM
CN Celacol MM 10P
CN Celacol MMPR
CN Celacol WA
CN Cellapret
CN Cellogran
CN Cellothyl
CN Cellulose methylate
CN Cellumeth
CN Cesca C 8556
CN Cesca MC 25S
CN Cesca MC 400
CN Cethylose
CN Cethytin
CN Culminal K 42
CN Culminal MC
CN Culminal MC 2000
CN Culminal MC 25S
CN Culminal MC 3000P
CN Culminal MC 3000PR
CN Culminal MC 40
CN Culminal MC 60S
CN Edisol M
CN EMP-H
CN Hi-SM 4000
CN Hydrolose
CN M 100
CN M 100 (cellulose derivative)
CN M 15
CN M 15 (cellulose derivative)
CN Marpolose 60SH50
CN Marpolose 90MP10000
CN Marpolose 90MP30000
CN Marpolose Ace
CN Marpolose EM 2000
CN Marpolose M 10000
CN Marpolose M 25
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 53568-34-6, 71812-19-6, 88402-84-0, 39384-65-1, 99638-59-2
MF C H4 O . x Unspecified
CI COM
PCT Manual registration, Polyother, Polyother only
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 9004-34-6
CMF Unspecified

CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 67-56-1
CMF C H4 O

H_3C-OH

8882 REFERENCES IN FILE CA (1967 TO DATE)
171 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8886 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:214950

REFERENCE 2: 134:212715

REFERENCE 3: 134:212610

REFERENCE 4: 134:212501

REFERENCE 5: 134:211797

REFERENCE 6: 134:211368

REFERENCE 7: 134:211291

REFERENCE 8: 134:210411

REFERENCE 9: 134:209545

REFERENCE 10: 134:209535

L55 ANSWER 10 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-65-3** REGISTRY
CN Cellulose, 2-hydroxypropyl methyl ether (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxypropyl methyl cellulose
CN 2-Hydroxypropyl methyl cellulose ether
CN 60SH4000F
CN 90SH15000S
CN Accel R 100
CN Benecel MP 363C
CN Benecel MP 943
CN Benecel MP 943W
CN Bermocoll E 411FQ
CN Celacol 15000DS
CN Celacol HPM 15000DS
CN Celacol HPM 450
CN Celacol HPM 5000
CN Cellulose hydroxypropyl methyl ether
CN Cesca HPC 50
CN Courlose HPM
CN Culminal 20000PFR
CN Culminal MHPC
CN Culminal MHPC 20000PFR
CN Culminal MHPC 20000PR
CN Culminal MHPC 2000S
CN Culminal MHPC 4000PFR
CN Culminal MHPC 6000
CN DP 1208
CN DP 1209

CN EM 1100
CN EM 1100 (cellulose derivative)
CN HPM 100DS
CN HPMC
CN HPMC 20000PV
CN HPMC 2208
CN HPMC-K 35LV
CN Hydroxypropyl methyl cellulose
CN Hydroxypropyl methyl cellulose ether
CN Hypromellose
CN Marpolose 60MP5
CN Marpolose 65MP400
CN Marpolose 65MP4000
CN Marpolose 90MP15000
CN Marpolose 90MP4000
CN Marpolose EMP-H
CN Marpolose MP 4000
CN MC 400
CN Mecellulose PMC 40U
CN Methocel 181
CN Methocel 20-231
CN Methocel 20-333
CN Methocel 227
CN Methocel 228
CN Methocel 240S
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 12673-53-9, 8063-82-9, 11106-33-5, 171544-38-0, 59029-31-1, 125053-98-7, 62683-26-5, 65607-39-8, 37341-76-7, 68073-10-9, 137397-89-8, 137397-90-1, 137397-91-2, 71373-07-4, 39363-71-8
MF C3 H8 O2 . x C H4 O . x Unspecified
CI COM
PCT Manual registration, Polyother, Polyother only
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

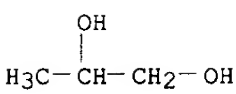
CM 2

CRN 67-56-1
CMF C H4 O

H_3C-OH

CM 3

CRN 57-55-6
CMF C3 H8 O2



6416 REFERENCES IN FILE CA (1967 TO DATE)
105 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6418 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212782

REFERENCE 2: 134:212738

REFERENCE 3: 134:212735

REFERENCE 4: 134:212734

REFERENCE 5: 134:212732

REFERENCE 6: 134:212715

REFERENCE 7: 134:212610

REFERENCE 8: 134:212572

REFERENCE 9: 134:209535

REFERENCE 10: 134:208487

L55 ANSWER 11 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-64-2** REGISTRY
CN Cellulose, 2-hydroxypropyl ether (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxypropyl cellulose
CN Aqualon Klucel L
CN Cellulose hydroxypropyl ether
CN EF 10
CN EF 10 (cellulose derivative)
CN Fuji HEC-SG 25F
CN G 4000HXL
CN HPC
CN HPC-E
CN HPC-E (cellulose derivative)
CN HPC-EF-G
CN HPC-H
CN HPC-L
CN HPC-LE-G
CN HPC-LG
CN HPC-LR
CN HPC-M
CN HPC-MF
CN HPC-MG
CN HPC-S
CN HPC-S (cellulose derivative)
CN HPC-SL
CN HPC-SSL
CN Hydropropyl cellulose
CN Hydroxypropyl cellulose
CN Hydroxypropyl cellulose ether
CN Hydroxypropyl ether of cellulose
CN Hyprolose
CN JK 491
CN Klucel
CN Klucel 98 HF-EP
CN Klucel 99 MF-EP

CN Klucel 99E
CN Klucel 99EF
CN Klucel 99G
CN Klucel 99GF-EP
CN Klucel 99M
CN Klucel E
CN Klucel E 5
CN Klucel EEL
CN Klucel EF
CN Klucel G
CN Klucel Gf
CN Klucel H
CN Klucel HF
CN Klucel HF-NF
CN Klucel HW
CN Klucel HXF
CN Klucel J
CN Klucel JF
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 9076-24-8, 173523-78-9, 65742-73-6, 78214-41-2, 150873-09-9, 192006-47-6, 193561-69-2, 210920-15-3
MF C3 H8 O2 . x Unspecified
CI COM
PCT Manual registration, Polyother, Polyother only
LC STN Files: AGRICOLA, AIDSLINE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TULSA, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

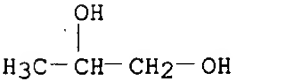
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 57-55-6
CMF C3 H8 O2



5687 REFERENCES IN FILE CA (1967 TO DATE)
146 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5691 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212782

REFERENCE 2: 134:212749

REFERENCE 3: 134:212738

REFERENCE 4: 134:212735

REFERENCE 5: 134:212734

REFERENCE 6: 134:212732

REFERENCE 7: 134:212726

REFERENCE 8: 134:212627

REFERENCE 9: 134:212501

REFERENCE 10: 134:211571

L55 ANSWER 12 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-62-0** REGISTRY
CN Cellulose, 2-hydroxyethyl ether (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxyethyl cellulose
CN 2-Hydroxyethyl cellulose ether
CN Admiral 3089FS
CN AH 15
CN AL 15
CN Aqualon HEC
CN AW 15
CN AW 15 (polysaccharide)
CN AX 15
CN BL 15
CN BL 15 (cellulose derivative)
CN Cellobond 25T
CN Cellobond 45000A
CN Cellobond HEC 15A
CN Cellobond HEC 400
CN Cellobond HEC 5000
CN Cellosize
CN Cellosize 4400H16
CN Cellosize DP 40
CN Cellosize HEC 4400
CN Cellosize HEC-QP 15000H
CN Cellosize HEC-QP 30000H
CN Cellosize HEC-QP 52000H
CN Cellosize HEC/QP-09-L
CN Cellosize OP 09
CN Cellosize QP
CN Cellosize QP 09H
CN Cellosize QP 10000
CN Cellosize QP 100M
CN Cellosize QP 100MH
CN Cellosize QP 1500
CN Cellosize QP 15000
CN Cellosize QP 15000H
CN Cellosize QP 15MH
CN Cellosize QP 3
CN Cellosize QP 300
CN Cellosize QP 30000
CN Cellosize QP 300H
CN Cellosize QP 40
CN Cellosize QP 40L
CN Cellosize QP 4400
CN Cellosize QP 4400H
CN Cellosize QP 52000
CN Cellosize QP 52000H
CN Cellosize QP 5200W1930X
CN Cellosize TJC 500
CN Cellosize UT 40
CN Cellosize WP
CN Cellosize WP 02W1062R
CN Cellosize WP 09
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for

DISPLAY
DR 12772-61-1, 9045-96-9, 163648-13-3, 173523-80-3, 97105-13-0, 72146-24-8, 86168-41-4, 53124-21-3, 53124-22-4, 53149-00-1, 168679-18-3, 189832-76-6
MF C2 H6 O2 . x Unspecified
CI COM
PCT Manual registration, Polyother, Polyother only
LC STN Files: AGRICOLA, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TULSA, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 107-21-1
CMF C2 H6 O2

HO—CH_2—CH_2—OH

6558 REFERENCES IN FILE CA (1967 TO DATE)
450 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6569 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212782

REFERENCE 2: 134:212715

REFERENCE 3: 134:212501

REFERENCE 4: 134:210360

REFERENCE 5: 134:209763

REFERENCE 6: 134:198138

REFERENCE 7: 134:197881

REFERENCE 8: 134:197129

REFERENCE 9: 134:194900

REFERENCE 10: 134:194686

L55 ANSWER 13 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-57-3** REGISTRY
CN Cellulose, ethyl ether (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Ampacet E/C
CN Aquacoat
CN Aquacoat EC 30D
CN Aquacoat ECD 30
CN Aquacoat ECD 30FMC

CN Aqualon NF
CN Cellulose ethyl
CN Cellulose ethylate
CN EC-N 100
CN ECN 10
CN EHEC X-high
CN ET 100
CN ET 100 (cellulose derivative)
CN Ethocel
CN Ethocel 10
CN Ethocel 100
CN Ethocel 150
CN Ethocel 350
CN Ethocel 7CP
CN Ethocel 890
CN Ethocel CP 10
CN Ethocel E
CN Ethocel E 50
CN Ethocel E 7
CN Ethocel HE350
CN Ethocel MED
CN Ethocel N 10
CN Ethocel N 100
CN Ethocel N 200
CN Ethocel N 7
CN Ethocel S 100
CN Ethocel S 20
CN Ethocel S 50
CN Ethocel STD
CN Ethocel STD 100
CN Ethocel STD 100CPS
CN Ethocel STD 100FP
CN Ethocel STD 4
CN Ethocel STD 45
CN Ethocel STD 45CPS
CN Ethocel STD 7CPS
CN Ethocel STDS 10CPS
CN Ethyl cellulose ether
CN Ethyl Cellulose N-200
CN Ethylcellulose
CN ETs
CN ETs (polysaccharide)
CN G 200
CN G 200 (polysaccharide)
CN G 50
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 11097-03-3, 166735-68-8, 57307-96-7, 51331-16-9
MF C2 H6 O . x Unspecified
CI COM
PCT Manual registration, Polyother, Polyother only
LC STN Files: AGRICOLA, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TULSA, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 64-17-5
CMF C2 H6 O

H_3C-CH_2-OH

6541 REFERENCES IN FILE CA (1967 TO DATE)
103 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6541 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:214930

REFERENCE 2: 134:214881

REFERENCE 3: 134:214368

REFERENCE 4: 134:212738

REFERENCE 5: 134:212735

REFERENCE 6: 134:212734

REFERENCE 7: 134:212733

REFERENCE 8: 134:212732

REFERENCE 9: 134:212502

REFERENCE 10: 134:212501

L55 ANSWER 14 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-38-0** REGISTRY
CN Cellulose, acetate hydrogen 1,2-benzenedicarboxylate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cellulose, acetate hydrogen phthalate (8CI)
CN Phthalic acid, ester with cellulose acetate (8CI)
OTHER NAMES:
CN Acetyl phthalyl cellulose
CN Aquacoat CPD
CN CAP
CN CAP-wako
CN Cellacefate
CN Cellacephate
CN Cellulose acetate monophthalate
CN Cellulose acetate phthalate
CN Cellulose acetate-phthalate mixed ester
CN Cellulose acetophthalate
CN Cellulose acetylphthalate
CN Cellulose phthalate acetate
CN KC 71
DR 8063-81-8, 9032-33-1, 55600-03-8, 37264-78-1
MF C8 H6 O4 . x C2 H4 O2 . x Unspecified
CI COM
PCT Manual registration
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MSDS-OHS, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)

Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

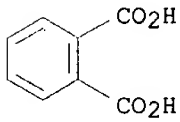
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

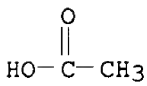
CM 2

CRN 88-99-3
CMF C8 H6 O4



CM 3

CRN 64-19-7
CMF C2 H4 O2



1211 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1211 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:212738

REFERENCE 2: 134:212735

REFERENCE 3: 134:212734

REFERENCE 4: 134:212730

REFERENCE 5: 134:209031

REFERENCE 6: 134:198113

REFERENCE 7: 134:198096

REFERENCE 8: 134:198085

REFERENCE 9: 134:198075

REFERENCE 10: 134:198054

L55 ANSWER 15 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-34-6** REGISTRY
CN Cellulose (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .alpha.-Cellulose
CN .beta.-Amylose

CN 3mAQUACEL
CN 402-2B
CN Alicell LV
CN Alpha Cel PB 25
CN Alphafloc
CN Arbocel
CN Arbocel B 00
CN Arbocel B 600/30
CN Arbocel B 800
CN Arbocel B 820C
CN Arbocel BC 1000
CN Arbocel BC 200
CN Arbocel BE 600
CN Arbocel BE 600/10
CN Arbocel BE 600/20
CN Arbocel BE 600/30
CN Arbocel BWW 40
CN Arbocel DC 1000
CN Arbocel FD 00
CN Arbocel FD 600/30
CN Arbocel FIC 200
CN Arbocel FT 40
CN Arbocel TF 30HG
CN Arbocel TP 40
CN Avicel
CN Avicel 101
CN Avicel 102
CN Avicel 2330
CN Avicel 2331
CN Avicel 955
CN Avicel CL 611
CN Avicel E 200
CN Avicel F 20
CN Avicel FD 100
CN Avicel FD 101
CN Avicel FD-F 20
CN Avicel M 06
CN Avicel M 15
CN Avicel M 25
CN Avicel PH 101
CN Avicel PH 102
CN Avicel PH 105
CN Avicel PH 200
CN Avicel PH 301
CN Avicel PH 302
CN Avicel PH-F 10
CN Avicel PH-F 20
CN Avicel PH-M 06
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 12656-52-9, 9012-19-5, 9037-50-7, 9076-30-6, 58968-67-5, 99331-82-5, 67016-75-5, 67016-76-6, 51395-76-7, 61991-21-7, 61991-22-8, 68073-05-2, 70225-79-5, 74623-16-8, 75398-83-3, 77907-70-1, 84503-75-3, 89468-66-6, 39394-43-9
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration, Polyother, Polyother only
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TULSA, ULIDAT, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
52402 REFERENCES IN FILE CA (1967 TO DATE)
6203 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
52441 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:216586

REFERENCE 2: 134:212793

REFERENCE 3: 134:212785

REFERENCE 4: 134:212782

REFERENCE 5: 134:212781

REFERENCE 6: 134:212780

REFERENCE 7: 134:212763

REFERENCE 8: 134:212738

REFERENCE 9: 134:212735

REFERENCE 10: 134:212734

L55 ANSWER 16 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9004-32-4** REGISTRY
CN Cellulose, carboxymethyl ether, sodium salt (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 12M31XP
CN 1400LC
CN 2000MH
CN 7H3SF
CN 7H3SX
CN 7H4XF
CN 9H4XF
CN A 0111
CN A 01H
CN A 01L
CN A 01M
CN A 02SH
CN A 10M
CN A 50M
CN AG Gum
CN AG Gum HG
CN AG Gum LV 1
CN AG Gum LV 2
CN AKU-W 515
CN Akucell 07071
CN Akucell AF 2205
CN Akucell AF 2805
CN Akucell AF 2881
CN Ambergum 1221
CN Ambergum 1521
CN Ambergum 1570
CN Ambergum 3021
CN Ambergum 99-3021
CN AOIH
CN Aquacide I
CN Aquacide II
CN Aqualon 12M31
CN Aqualon 7H
CN Aqualon 7HF
CN Aqualon 7LF-PH
CN Aqualon 7M2

CN Aqualon CMC 12M8
CN Aqualon CMC 7H
CN Aqualon CMC 7H4F
CN Aqualon CMC 7H4XF
CN Aqualon CMC 7HCF
CN Aqualon CMC 7HX
CN Aqualon CMC 7L
CN Aqualon CMC 7LT
CN Aqualon CMC 7M
CN Aqualon CMC 9H4F
CN Aquaplast
CN Aquasorb F-C
CN Aquasorb F-R
CN Aquasorb FC 1/16
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 12624-09-8, 9045-95-8, 9085-26-1, 54018-17-6, 55607-96-0, 50642-44-9, 37231-14-4, 37231-15-5, 73699-63-5, 80296-93-1, 82197-79-3, 81209-86-1, 117385-93-0, 198084-97-8, 247080-55-3
MF C2 H4 O3 . x Na . x Unspecified
CI COM
PCT Manual registration, Polyester, Polyester formed
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DETHERM*, DIOGENES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TULSA, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

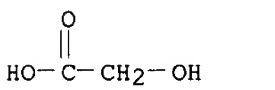
CM 1

CRN 9004-34-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 79-14-1
CMF C2 H4 O3



17224 REFERENCES IN FILE CA (1967 TO DATE)
598 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
17234 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:214967

REFERENCE 2: 134:212782

REFERENCE 3: 134:212759

REFERENCE 4: 134:212602

REFERENCE 5: 134:212502

REFERENCE 6: 134:209545

REFERENCE 7: 134:209497

REFERENCE 8: 134:209484

REFERENCE 9: 134:209065

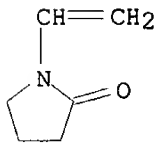
REFERENCE 10: 134:208974

L55 ANSWER 17 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **9003-39-8** REGISTRY
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Pyrrolidinone, 1-vinyl-, polymers (8CI)
OTHER NAMES:
CN 1-Vinyl-2-pyrrolidinone polymer
CN 1-Vinyl-2-pyrrolidone homopolymer
CN 1-Vinyl-2-pyrrolidone polymer
CN 143RP
CN Agent AT 717
CN Agrimer 30
CN Agrimer K 30
CN Albigen A
CN Aldacol Q
CN Antaron P 804
CN Antitox Vana
CN AT 717
CN B 7509
CN Bolinan
CN Cevian A 88036
CN Crospovidone
CN Divergan RS
CN Gaftex AE-K 15
CN Ganex P 804
CN Hemodesis
CN Hemodez
CN K 115
CN K 115 (vinyl polymer)
CN K 120
CN K 120 (vinyl polymer)
CN K 15
CN K 15 (polymer)
CN K 17
CN K 25
CN K 25 (surfactant)
CN K 30
CN K 60
CN K 60 (polymer)
CN K 90
CN Kollidon
CN Kollidon 12PF
CN Kollidon 17
CN Kollidon 17PF
CN Kollidon 25
CN Kollidon 30
CN Kollidon 90
CN Kollidon 90F
CN Kollidon CE 50/50
CN Kollidon K 17
CN Kollidon K 25
CN Kollidon K 30
CN Kollidon K 90
CN Kollidon K 90F
CN LFC
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 9015-62-7, 9080-59-5, 132778-04-2, 132778-05-3, 132834-20-9, 61932-72-7,

65931-56-8, 153631-61-9, 29386-94-5, 41724-41-8, 53026-73-6, 53026-74-7,
53200-27-4, 111214-46-1, 116404-61-6
MF (C6 H9 N O)x
CI PMS, COM
PCT Polyvinyl
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT,
APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS,
CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,
DETHERM*, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB,
IMSDIRECTORY, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PIRA, PROMT,
RTECS*, TOXLINE, TOXLIT, TULSA, USAN, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

CM 1

CRN 88-12-0
CMF C6 H9 N O



16666 REFERENCES IN FILE CA (1967 TO DATE)
711 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
16688 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:213211

REFERENCE 2: 134:212759

REFERENCE 3: 134:212739

REFERENCE 4: 134:212738

REFERENCE 5: 134:212735

REFERENCE 6: 134:212734

REFERENCE 7: 134:212732

REFERENCE 8: 134:212720

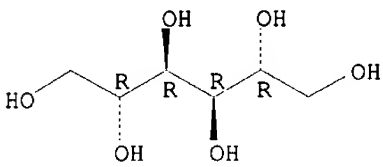
REFERENCE 9: 134:212715

REFERENCE 10: 134:212690

L55 ANSWER 18 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **69-65-8** REGISTRY
CN D-Mannitol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cordycepic acid (6CI, 7CI)
CN Mannitol, D- (8CI)
OTHER NAMES:
CN D-(-)-Mannitol
CN Diosmol
CN Isotol
CN Maniton S
CN Manna sugar
CN Mannidex
CN Mannigen

CN Mannistol
CN Mannit
CN Mannite
CN Mannitol
CN Mannitolum
CN Mannogem 2080
CN Osmitrol
CN Osmosal
FS STEREOSEARCH
DR 123897-58-5, 75398-80-0, 85085-15-0
MF C6 H14 O6
CI COM
LC STN Files: AGRICOLA, AIDSLINE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, TULSA, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



10331 REFERENCES IN FILE CA (1967 TO DATE)
246 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
10338 REFERENCES IN FILE CAPLUS (1967 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:212759

REFERENCE 2: 134:212756

REFERENCE 3: 134:212753

REFERENCE 4: 134:212743

REFERENCE 5: 134:212690

REFERENCE 6: 134:212628

REFERENCE 7: 134:212573

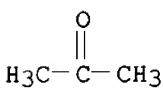
REFERENCE 8: 134:207323

REFERENCE 9: 134:204669

REFERENCE 10: 134:204605

L55 ANSWER 19 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **67-64-1** REGISTRY
CN 2-Propanone (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetone (8CI)
CN Methyl ketone (6CI)
OTHER NAMES:
CN .beta.-Ketopropane
CN Dimethyl ketone

CN Dimethylformaldehyde
CN Propanone
CN Pyroacetic ether
FS 3D CONCORD
MF C3 H6 O
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXLINE, TOXLIT, TRCTHERMO*, TULSA, ULIDAT, USAN, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



48269 REFERENCES IN FILE CA (1967 TO DATE)
494 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
48313 REFERENCES IN FILE CAPLUS (1967 TO DATE)
22 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:216603

REFERENCE 2: 134:216587

REFERENCE 3: 134:214874

REFERENCE 4: 134:214775

REFERENCE 5: 134:214714

REFERENCE 6: 134:214364

REFERENCE 7: 134:214001

REFERENCE 8: 134:212767

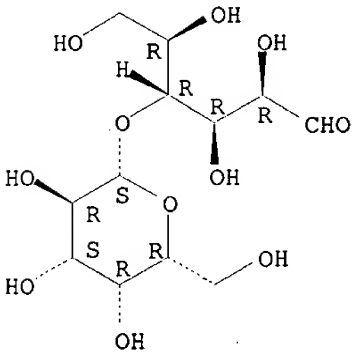
REFERENCE 9: 134:212752

REFERENCE 10: 134:212744

L55 ANSWER 20 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **63-42-3** REGISTRY
CN D-Glucose, 4-O-.beta.-D-galactopyranosyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Lactose (8CI)
OTHER NAMES:
CN (+)-Lactose
CN AHL
CN Aletobiose
CN D-(+)-Lactose
CN Fast-flo
CN Fast-Flo Lactose
CN Galactinum
CN Lactin
CN Lactin (carbohydrate)
CN Lactobiose
CN Lactose anhydrous

CN Lactose Fast-flo
CN Milk sugar
CN Osmolactan
CN Pharmatose 21
CN Pharmatose 325M
CN Pharmatose 450M
CN Saccharum lactin
CN Tablettose
CN Zeparox EP
AR 16984-38-6
FS STEREOSEARCH
DR 1336-90-9, 73824-63-2, 89466-76-2, 35396-14-6
MF C12 H22 O11
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, TULSA, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (+).



15671 REFERENCES IN FILE CA (1967 TO DATE)
467 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
15683 REFERENCES IN FILE CAPLUS (1967 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:212690

REFERENCE 2: 134:212627

REFERENCE 3: 134:212617

REFERENCE 4: 134:212604

REFERENCE 5: 134:212565

REFERENCE 6: 134:212521

REFERENCE 7: 134:209761

REFERENCE 8: 134:206942

REFERENCE 9: 134:206874

REFERENCE 10: 134:206758

L55 ANSWER 21 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **57-11-4** REGISTRY
CN Octadecanoic acid (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Heptadecanecarboxylic acid
CN 17FA
CN 400JB9103-88
CN A 1760
CN Adeka Fatty Acid SA 910
CN Barolub FTA
CN Century 1210
CN Century 1220
CN Century 1230
CN Century 1240
CN Edenor HT-JG 60
CN Edenor ST 1
CN Edenor ST 20
CN Emersol 120
CN Emersol 153NF
CN Emersol 6349
CN F 3
CN F 3 (lubricant)
CN Humko Industrene R
CN Hydrofol Acid 150
CN Hydrofol Acid 1895
CN Hystrene 4516
CN Hystrene 80
CN Hystrene 9718
CN Hystrene 9718NF
CN Hystrene 9718NFFG
CN Hystrene S 97
CN Hystrene T 70
CN Industrene 8718
CN Industrene 9018
CN Industrene R
CN Kam 1000
CN Kam 2000
CN Kam 3000
CN Kortacid 1895
CN Loxiol G 20
CN Lunac 30
CN Lunac S 20
CN Lunac S 30
CN Lunac S 40
CN Lunac S 50
CN Lunac S 90
CN Lunac S 90KC
CN Lunac S 98
CN Lunac YA
CN n-Octadecanoic acid
CN NAA 173
CN NAA 180
CN Neo-Fat 18
CN Neo-Fat 18-53
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS 3D CONCORD
DR 8013-28-3, 8023-06-1, 8037-40-9, 8037-83-0, 8039-51-8, 8039-52-9, 8039-53-0, 8039-54-1, 58392-66-8, 134503-33-6, 82497-27-6, 39390-61-9, 197923-10-7
MF C18 H36 O2
CI COM
LC STN Files: AGRICOLA, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE,

GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXLINE, TOXLIT, TRCTHERMO*, TULSA, USAN, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

$HO_2C-(CH_2)_{16}-Me$

31192 REFERENCES IN FILE CA (1967 TO DATE)
2290 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
31229 REFERENCES IN FILE CAPLUS (1967 TO DATE)
19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:216320

REFERENCE 2: 134:216299

REFERENCE 3: 134:214903

REFERENCE 4: 134:213078

REFERENCE 5: 134:212760

REFERENCE 6: 134:212489

REFERENCE 7: 134:212475

REFERENCE 8: 134:212470

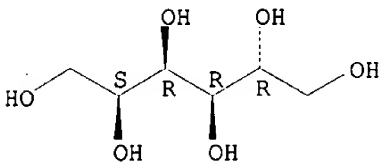
REFERENCE 9: 134:211771

REFERENCE 10: 134:211715

L55 ANSWER 22 OF 22 REGISTRY COPYRIGHT 2001 ACS
RN **50-70-4** REGISTRY
CN D-Glucitol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glucitol, D- (8CI)
CN Sorbitol (7CI)
OTHER NAMES:
CN (-)-Sorbitol
CN C*Sorbidex
CN Cholaxine
CN D-(-)-Sorbitol
CN D-Sorbitol
CN D-Sorbol
CN Diakarmon
CN Esasorb
CN Foodol D 70
CN Glucarine
CN Glucarine (sorbitol syrup)
CN Glucitol
CN Karion
CN Karion (carbohydrate)
CN Karion instant
CN L-Gulitol
CN Multitol
CN Neosorb
CN Neosorb 20/60DC
CN Neosorb 70/02
CN Neosorb 70/70
CN Neosorb P 20/60

CN Neosorb P 60
CN Nivitin
CN Sionit
CN Sionit K
CN Sionite
CN Sionon
CN Siosan
CN Sorbex M
CN Sorbex R
CN Sorbex Rp
CN Sorbex S
CN Sorbex X
CN Sorbilande
CN Sorbit
CN Sorbit D 70
CN Sorbit L 70
CN Sorbit S
CN Sorbit W 70
CN Sorbit W-Powder
CN Sorbit WP
CN Sorbite
CN Sorbitol F
CN Sorbitol FP
CN Sorbitol syrup C
CN Sorbo
CN Sorbol
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS STEREOSEARCH
DR 8013-15-8, 8014-89-9, 8036-93-9, 8042-39-5, 8045-74-7, 8046-05-7, 63800-20-4, 15060-73-8, 98201-93-5, 3959-53-3, 36134-87-9, 75398-79-7
MF C6 H14 O6
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, TULSA, USAN, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



12589 REFERENCES IN FILE CA (1967 TO DATE)
1071 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12604 REFERENCES IN FILE CAPLUS (1967 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 134:212759

REFERENCE 2: 134:212739

REFERENCE 3: 134:212489

REFERENCE 4: 134:209761

REFERENCE 5: 134:208122

REFERENCE 6: 134:206822

REFERENCE 7: 134:204956

REFERENCE 8: 134:204906

REFERENCE 9: 134:204751

REFERENCE 10: 134:202698

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FILE 'USPATFULL' ENTERED AT 08:09:18 ON 30 MAR 2001
CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Mar 2001 (20010327/PD)
FILE LAST UPDATED: 27 Mar 2001 (20010327/ED)
HIGHEST PATENT NUMBER: US6209132
CA INDEXING IS CURRENT THROUGH 27 Mar 2001 (20010327/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Mar 2001 (20010327/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2000
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2000

>>> Page images are available for patents from 1/1/1997. Current <<<
>>> week patent text is typically loaded by Thursday morning and <<<
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>>> Image data for the /FA field are available the following week. <<<

>>> Complete CA file indexing for chemical patents (or equivalents) <<<
>>> is included in file records. A thesaurus is available for the <<<
>>> USPTO Manual of Classifications in the /NCL, /INCL, and /RPCL <<<
>>> fields. This thesaurus includes catchword terms from the <<<
>>> USPTO/MOC subject headings and subheadings. Thesauri are also <<<
>>> available for the WIPO International Patent Classification <<<
>>> (IPC) Manuals, editions 1-6, in the /IC1, /IC2, /IC3, /IC4, <<<
>>> /IC5, and /IC (/IC6) fields, respectively. The thesauri in <<<
>>> the /IC5 and /IC fields include the corresponding catchword <<<
>>> terms from the IPC subject headings and subheadings. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d his 156-

(FILE 'REGISTRY' ENTERED AT 08:00:21 ON 30 MAR 2001)

FILE 'USPATFULL' ENTERED AT 08:01:19 ON 30 MAR 2001
L56 64 S L13
L57 53 S L56 AND (PD<=19970815 OR PRD<19970815 OR AD<19970815)
L58 25 S L57 AND (ACETONE OR L17)
L59 0 S L58 AND L24-L32
L60 18 S L58 AND (POVIDON? OR ?CELLULOS? OR LACTOSE OR MANNITOL OR SOR
L61 15 S L58 AND EXCIPIENT?
L62 18 S L60,L61
L63 4 S L62 AND SPRAY DRY?
L64 5 S L62 AND SPRAY DRI?
L65 0 S L62 AND SPRAYDR?
L66 5 S L63,L64
L67 13 S L62 NOT L66

FILE 'USPATFULL' ENTERED AT 08:09:18 ON 30 MAR 2001

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L66 ANSWER 1 OF 5 USPATFULL
AN 91:36516 USPATFULL
TI Process for preparing **cefuroxime axetil**
IN Crisp, Harold A., Harrow Weald, England
Clayton, John C., Eastcote, England
Elliott, Leonard G., Great Urswick, England
Wilson, Edward M., St. John's Close, England
PA Glaxo Group Limited, England (non-U.S. corporation)
PI US 5013833 19910507 <--
AI US 1988-258908 19881018 (7) <--
RLI Division of Ser. No. US 1986-938140, filed on 4 Dec 1986, now patented, Pat. No. US 4820833, issued on 11 Apr 1989 which is a continuation of Ser. No. US 1985-781505, filed on 30 Sep 1985, now abandoned which is a continuation of Ser. No. US 1985-711559, filed on 14 Mar 1985, now abandoned which is a continuation of Ser. No. US 1984-635797, filed on 30 Jul 1984, now abandoned which is a continuation of Ser. No. US 1983-518671, filed on 29 Jul 1983, now abandoned
PRAI GB 1982-22019 19820730 <--
DT Utility
EXNAM Primary Examiner: Rizzo, Nicholas S.
LREP Bacon & Thomas
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 692
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level of bioavailability on oral or rectal administration.

Methods of preparing the product are also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.

Also disclosed are pharmaceutical compositions containing the product and methods for its use in medicine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Process for preparing **cefuroxime axetil**
PI US 5013833 19910507 <--
AI US 1988-258908 19881018 (7) <--
PRAI GB 1982-22019 19820730 <--
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level. .
.
AB . . . also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.
SUMM This invention relates to a novel, amorphous form of the 1-acetoxyethyl ester of cefuroxime(**cefuroxime axetil**), to a process for the preparation thereof, to a composition containing it and to its use in medicine.
SUMM Of the esters described in British Patent Specification No. 1571683, we have found **cefuroxime axetil** to be of particular interest. The processes for the preparation of the above ester

exemplified in British Patent Specification No.. . .

SUMM In view of past experience in the cephalosporin field, we first prepared **cefuroxime axetil** for commercial evaluation in substantially pure, crystalline form. We have however surprisingly found that substantially pure, crystalline **cefuroxime axetil** does not have the best balance of properties for commercial use and that, contrary to previous experience in the cephalosphor in field, **cefuroxime axetil** is advantageously used in a highly pure, substantially amorphous form. We have thus established that highly pure **cefuroxime axetil** when in substantially amorphous form has higher bioavailability upon oral administration than when in crystalline form and that moreover the amorphous form of **cefuroxime axetil** has adequate chemical stability upon storage. This is despite the known tendency for amorphous materials to have inferior chemical stability. . . known tendency for highly pure amorphous materials to crystallise. Thus, unlike previous cephalospor compounds which have been developed for commercialisation, **cefuroxime axetil** is advantageously prepared and used in highly pure amorphous form rather than in crystalline form.

SUMM According to one aspect of the present invention, there is provided **cefuroxime axetil** in highly pure, substantially amorphous form.

SUMM The **cefuroxime axetil** in accordance with the invention preferably contains less than 5% mass/mass (m/m), advantageously less than 3% m/m, of impurities. It. . . `impurities` are to be understood as not including residual solvents remaining from the process used in the preparation of the **cefuroxime axetil** of the invention. Any residual solvent present will desirably only be present in less than 6% m/m and most preferably. . .

SUMM Typical impurities which may be present are the .DELTA..sup.2 -isomers of **cefuroxime axetil** and the corresponding E-isomers of **cefuroxime axetil**.

SUMM The **cefuroxime axetil** ester in accordance with the invention is preferably essentially free from crystalline material.

SUMM **Cefuroxime axetil** possesses an asymmetric carbon atom at the 1-position of the 1-acetoxyethyl group and can therefore exist in the form of R and S isomers and mixtures thereof. The amorphous **cefuroxime axetil** ester according to the invention is preferably in the form of a mixture of its R and S isomers, such. . .

SUMM The **cefuroxime axetil** of the invention desirably has an E.sub.1 cm.sup.1% at its .lambda..sub.max in methanol, when corrected for any solvent content, of from about 395 to 415. In addition, the **cefuroxime axetil** of the invention having an R to S isomer ratio of from 0.9:1 to 1.1:1, particularly of about 1:1 desirably. . . 1 and 2 of the accompanying drawings are respectively infra-red and n.m.r. spectra for specimens of highly pure, substantially amorphous **cefuroxime axetil** in accordance with the invention.

SUMM After absorption **cefuroxime axetil** is converted into the parent antibiotic acid cefuroxime which is known to exhibit high antibacterial activity against a broad range of gram-positive and gram-negative organisms. **Cefuroxime axetil** is thus useful in the oral or rectal treatment of a variety of diseases or infections caused by pathogenic bacteria.

SUMM The **cefuroxime axetil** according to the invention is conveniently prepared by a process which constitutes a further feature of the present invention and which comprises recovering **cefuroxime axetil** from a solution thereof under conditions whereby a highly pure, substantially amorphous product is obtained.

SUMM Techniques which may be employed to recover substantially amorphous **cefuroxime axetil** from the solution thereof include those wherein solvent is removed from the solution, preferably rapidly, and the product deposited and. . . wherein the product is precipitated from solution. Methods involving the use of these procedures which have been found satisfactory include **spray**

drying, roller drying, solvent precipitation and freeze drying.

SUMM Solvents for **cefuroxime axetil** will be chosen according to the technique and conditions to be employed. Suitable solvents for dissolving **cefuroxime axetil** to form solutions from which recovery is enabled include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM The concentration of **cefuroxime axetil** in the solvent is with advantage is high as possible, commensurate with a substantially amorphous product being obtained, preferred concentrations being greater than 1% m/m, preferably greater than 10% m/m. The maximum concentration of the **cefuroxime axetil** in the solvent will depend upon the solvent used and in general will be less than 30% m/m. For example, the concentration of **cefuroxime axetil** in **acetone** will conveniently lie within the range 10 to 20% m/m. The solvents may if desired be heated as in aid. .

SUMM In general, we have found that the **cefuroxime axetil** has sufficient heat stability to withstand **spray drying** and accordingly **spray drying** is a preferred method of effecting recovery. **Spray drying** systems can be operated in known manner to obtain an amorphous product essentially free from crystalline material and free from particulate contaminants. Closed cycle **spray drying** systems in which the drying medium is recycled are particularly safe and economic for use in obtaining the product of. . .

SUMM When employing **spray drying**, suitable solvents for dissolving **cefuroxime axetil** prior to **spray drying** include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; esters, e.g. methyl. . .

SUMM . . . inert gases such as nitrogen, argon and carbon dioxide being preferred in this case. The gas inlet temperature to the **spray dryer** will be chosen according to the solvent used, but may for example be in the range 50.degree.-140.degree. C. preferably 60.degree.-125.degree.. . .

SUMM The use of rapid evaporation techniques, in particular the use of **spray drying** also leads particularly readily to the formation, under appropriate conditions, of products having a consistent range of particle sizes. The product from **spray drying** has the form of hollow microspheres which can conveniently be compounded into pharmaceutical compositions.

SUMM When employing roller drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM When employing solvent precipitation, suitable solvents from which the **cefuroxime axetil** may be precipitated include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . . this gives a homogeneous phase. Precipitation may be effected by the addition of appropriate quantities of a non-solvent for the **cefuroxime axetil**. Suitable non-solvents include water, alkanes and mixtures of alkanes, e.g. hexane or medium boiling range petrol (e.g. 60.degree.-80.degree. C.), ethers,. . . at least partially miscible and preferably fully miscible. Typical combinations of solvent and non-solvent are dichloromethane/isopropyl ether, ethyl acetate/petrol and **acetone**/water. The solid should be removed from solution as quickly as possible and dried as quickly as possible to avoid formation. . .

SUMM . . . technique of solvent precipitation may usefully be applied to the reaction mixture remaining after an esterification reaction in which

the **cefuroxime axetil** has been formed in order to obtain amorphous **cefuroxime axetil** directly. This may be achieved by the addition of a solvent e.g. an ester such as ethyl acetate to the. . .

SUMM When employing freeze-drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include dioxan and t-butanol. The temperature at which the recovery will be effected will depend upon the. . .

SUMM In order to obtain **cefuroxime axetil** ester in highly pure form by the above techniques it is necessary to employ a starting material of suitable purity. . .

SUMM The solution from which the **cefuroxime axetil** is recovered preferably contains a mixture of both R- and S- isomers, whereby the product is obtained as a mixture. . . . general, the R/S isomer ratio of the product in solution is exactly reflected in the final product obtained e.g. by **spray drying**, and this ratio for the final product can accordingly be controlled if desired by adjustment of the R/S isomer ratio. . .

SUMM The **cefuroxime axetil** ester according to the invention may be formulated for oral (including buccal) or rectal administration.

SUMM . . . Such pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable **excipients** such as binding agents e.g. pregelatinised maize starch, polyvinyl-pyrrolidone or hydroxypropyl-methyl-**cellulose**; fillers e.g. starch, **lactose**, micro-crystalline **cellulose** or calcium phosphates; lubricants e.g. magnesium **stearate**, hydrogenated vegetable oils, talc, silica, polyethyleneglycols; disintegrants e.g. potato starch or sodium **starch glycolate**; or wetting agents e.g. sodium lauryl sulphate. Flow aids e.g. silicon dioxide may also be used if desired. The tablets. . .

SUMM The preparation of a composition suitable for forming into tablets, capsules or granules may also be achieved by **spray-drying** or roller drying a suspension of pure amorphous **cefuroxime axetil** with the **excipients** appropriate for the said tablets, capsules or granules.

SUMM . . . liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents e.g. sorbitol syrup, methyl **cellulose** or hydrogenated edible fats and oils such as hydrogenated castor oil; emulsifying or thickening agents e.g. lecithin, aluminium **stearates** or acacia; non-aqueous vehicles e.g. almond oil, fractionated coconut oil, oily esters or ethyl alcohol; and preservatives e.g. methyl or. . .

SUMM The **cefuroxime axetil** of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository. . .

SUMM In a further aspect therefore the invention provides a pharmaceutical composition comprising **cefuroxime axetil** in highly pure, substantially amorphous form, in admixture with one or more pharmaceutical carriers and/or **excipients**. Such compositions are preferably adapted for absorption via the gastrointestinal tract, e.g. for oral administration. In a preferred embodiment, such. . .

SUMM . . . comprises administering to the said body orally or rectally an effective amount of a highly pure, substantially amorphous form of **cefuroxime axetil**.

SUMM The following non-limiting Examples illustrate the invention. In all these Examples, the **cefuroxime axetil** starting materials used were in highly pure crystalline form. Such starting materials may for example be obtained by processes as described in British Patent No. 1571683, or may alternatively be prepared by the crystallisation of highly pure **cefuroxime axetil** from an organic solvent, for example an ester such as ethyl acetate in admixture with an ether such as isopropyl. . .

SUMM . . . by hydrolysis in situ at a temperature of +10.degree. to +30.degree. C. and crystallisation by addition of sodium

2-ethylhexanoate in **acetone** or methyl acetate as solvent.

DETD Crystalline **Cefuroxime Axetil**

DETD . . . washed with 2:1 diisopropyl ether/ethyl acetate (150 ml) and dried for a weekend in vacuo at 50.degree. to give crystalline **cefuroxime axetil** (19.3 g).

DETD A 10% m/v **acetone** solution of a mixture of R and S isomers of **cefuroxime axetil** was put through a Niro Mobile Minor **Spray Drier**, supplied by Niro Copenhagen, Denmark, using air as the drying gas and a rotary atomizer running at about 35,000 rpm. The gas inlet and outlet temperatures were 124.degree. and 70.degree. respectively A recovery of 75% m/m of **spray dried** product was obtained. The microscopic appearance was typical for a **spray dried** product (hollow spheres). Assay by HPLC was 97% m/m and impurities by HPLC 2.0% m/m, both calculated to dry from. . .

DETD A mixture of R and S isomers of **cefuroxime axetil** (20.25 g) was dissolved in **acetone** (200 ml) at ambient temperature. The solution was clarified through sintered glass and pumped through a two fluid atomizer jet, using nitrogen under 1 kg/cm.sup.2 as the atomising fluid, into the glass drying chamber of a Mini Spray HO **spray drying** apparatus using an approximately 50:50 mixture of air and nitrogen as the drying gas. The gas inlet and outlet temperatures were 75.degree. and 55.degree. respectively. The recovery was 14.1 g (70.5%) of amorphous material containing 1.1% m/m **acetone** (GLC). Impurities (by HPLC) 1.7% m/m including 0.2% m/m ceph-2-em compound. Isomer ratio 1.03:1. .nu..sub.max (Nujol) similar to that shown. . .

DETD A 15% **acetone** solution of **cefuroxime axetil** (ca 1:1 mixture of R and S isomers) was put through a closed cycle **spray dryer** using nitrogen as the recycling gas and a rotating wheel atomiser running at 24,000 rpm. The gas inlet and outlet temperatures were 105.degree. and 70.degree. respectively. The recycling gas was cooled to remove most of the evaporated **acetone.** Recovery of amorphous product was 90% with an **acetone** content of 1.0% m/m (GLC), water 0.7% m/m (Karl Fischer), HPLC impurity level 1.3% m/m. Infrared (Nujol) (KBr plates) and. . .

DETD Further Examples 4 to 17 illustrating the preparation of amorphous **cefuroxime axetil** are given in the following Table. The process of these examples was similar to that of Example 2. The Nujol. . .

DETD

Ex No.	Solvent	Inlet Temp .degree.C.	Outlet Temp .degree.C.
4.	**Acetone**/water	62	55
5.	Industrial methylated spirit	80	70
6.	Acetonitrile	72	63
7.	Tetrahydrofuran	75	65
8.	Methylacetate	63	55
9.	Chloroform (water set)	64	58
10.	**Acetone**/water	70	50
11.	Ethylacetate/water	72	64
12.	Methylacetate/water	64	57
13.	Methanol/water	67-70	55-59
14.	Methanol/**acetone**	63	54
15.	Ethanol/**acetone**	83	65
16.	**Acetone**/methylacetate	63	54
17.	**Acetone**	85-90	75

DETD A solution of purified crystalline cefuroxime 1-acetoxyethyl ester (isomer A) (77 g) in **acetone** (1.8 liters) at 45.degree. was **spray dried** as in Example 2 through a two fluid atomizer nozzle with a nitrogen atomizing pressure of 0.5 kg/cm.sup.2. The gas inlet temperature was 85.degree.-90.degree. and the outlet temperature ca 75.degree.. The product (39 g) had an **acetone** content of 0.15% m/m and impurities by HPLC of 2.8% m/m. The infrared spectrum (Nujol) confirmed the amorphous nature of. . .

DETD A mixture of the R and S isomers of **cefuroxime axetil** (10 g) was dissolved in hot **acetone** (70 ml) and evaporated in vacuo to a froth. This was broken up and dried overnight in vacuo at 40.degree. to give 9.8 g of **cefuroxime axetil** which was shown by IR (Nujol) (which was similar to that in FIG. 1) and microscopic examination to be amorphous. The **acetone** content (GLC) was 2.9%. Impurities by HPLC were 3.4% m/m and the isomer ratio was 1.14:1.

DETD Following the above procedure, pure amorphous **cefuroxime axetil** was also obtained using IMS, methanol and ethyl acetate as solvents.

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (5 g) was dissolved in boiling ethylacetate (200 ml) and concentrated at atmospheric pressure to 70 ml. The solution was. . . displacement washed with petroleum ether (bp. 60.degree.-80.degree.) and dried overnight in vacuo at 50.degree. to give 4.5 g of amorphous **cefuroxime axetil**. Solvent content (GLC) 0.25% m/m; [.alpha.].sub.D (1% in dioxan) +39.degree.; E.sub.1 cm.sup.1% (MeOH) 388. Microscopic examination confirmed the amorphous nature. . .

DETD A ca 1:1 mixture of the R and S isomers of **Cefuroxime axetil** (6 g) was dissolved in boiling dichloromethane (240 ml), allowed to cool and filtered. The filtrate was distilled to a. . . filtered, washed with di-isopropyl ether (100 ml) and dried overnight in vacuo at 50.degree. to give 5.5 g of amorphous **cefuroxime axetil**. Microscopic examination suggested <1% crystalline material. [.alpha.].sub.D (1% dioxan)+36.degree., D.sub.1 cm.sup.1% 387 (MeOH) Solvent content (GLC), 1%.

DETD . . . nitrogen was bubbled in at 12 l min.sup.-1. A solution of a mixture of the R and S isomers of **cefuroxime axetil** (200 g) dissolved in a warm (45.degree.) mixture of **acetone** (600 ml) and water (66 ml) was then added with the aid of a peristaltic pump at a constant rate over 13 minutes into the vortex of the water. The precipitated amorphous **cefuroxime axetil** was carried through the horizontal aperture as a froth and collected. The amorphous **cefuroxime axetil** product was harvested immediately and dried to constant weight in vacuo at 55.degree. to yield 170 g. Solvent content (GLC)<0.01. . .

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (100 g) was dissolved by stirring in **acetone** (1 l) and warming to 40.degree. The rollers of a drier were heated to 75.degree. , steam (two bar pressure). . . jacket and 737 mm vacuum applied to the apparatus. Using a roller speed of 1.75 rpm the prepared solution of **cefuroxime axetil** was sucked in at a rate of ca 200 ml/min. The product was knifed from the rollers and collected in. . .

DETD A solution of a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (10 g) in dioxan (100 ml) was freeze dried to give the product (10.7 g) which contained dioxan 5.5% m/m. . .

DETD . . . of petrol (105 ml) and ethyl acetate (12 ml) followed by petrol (118 ml). Drying at 40.degree. in vacuo gave **cefuroxime axetil** 17.9 g: Solvents (GLC), ethylacetate 1.6%, petrol 1.5%; impurities by HPLC 4.1% m/m, isomer ratio 1.06:1; E.sub.1 cm.sup.1% (MeOH) 364.. . .

DETD **Acetone** (2000 ml), water (324 ml) and IMS (36 ml) were added to a stirred flask followed by a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (600 g). The contents of the

flask were heated to 42.degree. and stirred until the solid dissolved. Immediately prior to. . .

DETD Water (850 ml/min) and the **cefuroxime axetil** solution (115 ml/min) was added simultaneously into the turbulent zone in the precipitator. The overflow from the precipitator was directed. .

DETD . . . dried in vacuo at 45.degree. until the moisture content was reduced to less than 1% to yield 410 g of **cefuroxime axetil**.

DETD

Composition	mg/tablet
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Starch 1500 (Colorcon, Inc) (Pregelatinised starch)	161.5
Sodium **Starch Glycolate**	20.0
Sodium Lauryl Sulphate	10.0
Polyethylene glycol 6000 (Micronized)	7.5
Silicon Dioxide	1.0
Total weight	500.0

DETD The polyethylene glycol, sodium lauryl sulphate, sodium **starch glycolate** and silicon dioxide were passed through a 60 mesh screen and blended with a small quantity of the active ingredient.. .

DETD The tablet may then be film coated with **cellulose** derivatives with plasticisers, colouring agents and preservatives if necessary, using aqueous or organic solvent methods.

DETD

Composition	mg/capsule
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Microcrystalline **cellulose**	24.75
Hydrogenated Vegetable Oil	4.0
Sodium Lauryl Sulphate	9.0
Silicon Dioxide	1.25

DETD

Cefuroxime axetil according to the invention	300	mg
Sodium lauryl sulphate	25	mg
Hydroxypropyl-methyl-**cellulose**	90	mg
Spray dried orange flavour	150	mg
Castor sugar to	2220	mg

DETD The sodium lauryl sulphate, hydroxypropylmethyl-**cellulose** and flavour were triturated with the active ingredient. This blend was then further blended with castor sugar, adding the latter. . .

DETD

Cefuroxime axetil according to	300	mg

the invention

Lecithin	35	mg
Butylhydroxybenzoate	2	mg
Aluminium monostearate	25	mg
Aluminium distearate	25	mg
Hydrogenated castor oil	17.5	mg

Liquid flavor. . .

DETD Some of the coconut oil was heated, then the lecithin, butylhydroxybenzoate aluminum **stearates**, hydrogenated castor oil, icing sugar and sodium chloride were added to the oil with mixing.

DETD The mixture was cooled and the **cefuroxime axetil** and flavour added. The remainder of the required coconut oil was then added and the preparation was mixed and refined.

CLM What is claimed:

1. A process for the preparation of highly pure **cefuroxime axetil** containing less than 5% m/m impurities and in predominantly amorphous form which comprises recovering **cefuroxime axetil** from a solution thereof which contains an organic solvent selected from the group consisting of ketones, alcohols, acetonitrile, tetrahydrofuran, dioxan,. . .

2. The process of claim 1 wherein the concentration of **cefuroxime axetil** in the solution prior to recovery is at least 1% m/m.

3. The process of claim 1 wherein the concentration of **cefuroxime axetil** in the solution prior to recovery is at least 10% m/m.

IT 64-17-5, uses and miscellaneous 67-56-1, uses and miscellaneous **67-64-1**, uses and miscellaneous 67-66-3, uses and miscellaneous 75-05-8, uses and miscellaneous 75-09-2, uses and miscellaneous 79-20-9 108-20-3 109-99-9, uses and miscellaneous 123-91-1, uses and miscellaneous 141-78-6, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)

IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)

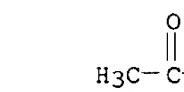
IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)

IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)

IT **67-64-1**, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)

RN 67-64-1 USPATFULL

CN 2-Propanone (9CI) (CA INDEX NAME)

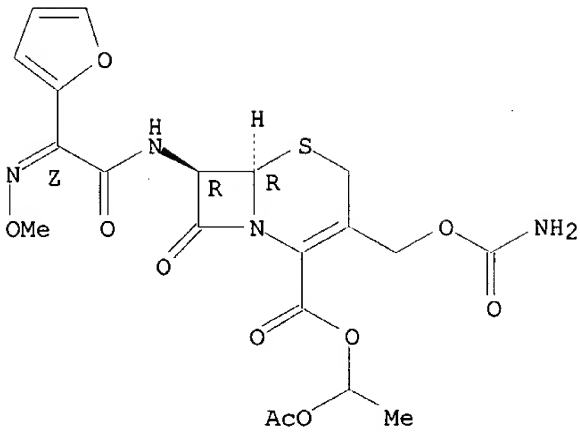


IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)

RN 64544-07-6 USPATFULL

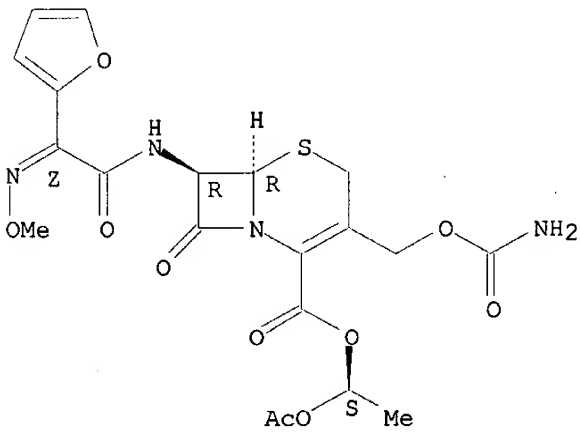
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



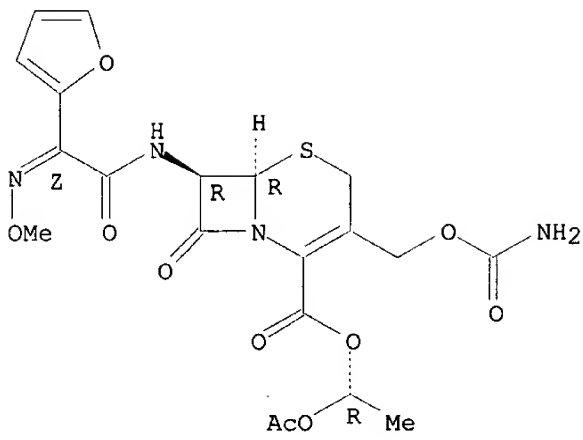
IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)
RN 64599-29-7 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1S)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)
RN 64599-28-6 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1R)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L66 ANSWER 2 OF 5 USPATFULL
AN 91:15274 USPATFULL
TI Process for preparation of cefuroxime ester
IN Crisp, Harold A., Harrow Weald, England
Clayton, John C., Eastcote, Pinner, England
Wilson, Edward M., St. John's Close, Penn, England
PA Galaxo Group Limited, London, England (non-U.S. corporation)
PI US 4994567 19910219 <--
AI US 1988-258886 19881018 (7) <--
DCD 20060411
RLI Division of Ser. No. US 1986-938140, filed on 4 Dec 1986, now patented, Pat. No. US 4820833 which is a continuation of Ser. No. US 1985-781505, filed on 30 Sep 1985, now abandoned which is a continuation of Ser. No. US 1985-711559, filed on 14 Mar 1985, now abandoned which is a continuation of Ser. No. US 1984-635797, filed on 30 Jul 1984, now abandoned which is a continuation of Ser. No. US 1983-518671, filed on 29 Jul 1983, now abandoned
PRAI GB 1982-22019 19820730 <--
DT Utility
EXNAM Primary Examiner: Rizzo, Nicholas S.
LREP Bacon & Thomas
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 701
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level of bioavailability on oral or rectal administration.

Methods of preparing the product are also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.

Also disclosed are pharmaceutical compositions containing the product and methods for its use in medicine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4994567 19910219 <--
AI US 1988-258886 19881018 (7) <--
PRAI GB 1982-22019 19820730 <--
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime

1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level. . .

AB . . . also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.

SUMM This invention relates to a novel, amorphous form of the 1-acetoxyethyl ester of cefuroxime(**cefuroxime axetil**), to a process for the preparation thereof, to a composition containing it and to its use in medicine.

SUMM Of the esters described in British Patent Specification No. 1571683, we have found **cefuroxime axetil** to be of particular interest. The processes for the preparation of the above ester exemplified in British Patent Specification No.. . .

SUMM In view of past experience in the cephalosporin field, we first prepared **cefuroxime axetil** for commercial evaluation in substantially pure, crystalline form. We have however surprisingly found that substantially pure, crystalline **cefuroxime axetil** does not have the best balance of properties for commercial use and that, contrary to previous experience in the cephalosporin field, **cefuroxime axetil** is advantageously used in a highly pure, substantially amorphous form. We have thus established that highly pure **cefuroxime axetil** when in substantially amorphous form has higher bioavailability upon oral administration than when in crystalline form and that moreover the amorphous form of **cefuroxime axetil** has adequate chemical stability upon storage. This is despite the known tendency for amorphous materials to have inferior chemical stability. . . known tendency for highly pure amorphous materials to crystallise. Thus, unlike previous cephalosporin compounds which have been developed for commercialisation, **cefuroxime axetil** is advantageously prepared and used in highly pure amorphous form rather than in crystalline form.

SUMM According to one aspect of the present invention, there is provided **cefuroxime axetil** in highly pure, substantially amorphous form.

SUMM The **cefuroxime axetil** in accordance with the invention preferably contains less than 5% mass/mass (m/m), advantageously less than 3% m/m, of impurities. It. . . 'impurities' are to be understood as not including residual solvents remaining from the process used in the preparation of the **cefuroxime axetil** of the invention. Any residual solvent present will desirably only be present in less than 6% m/m and most preferably. . .

SUMM Typical impurities which may be present are the .DELTA..sup.2 -isomers of **cefuroxime axetil** and the corresponding E-isomers of **cefuroxime axetil**.

SUMM The **cefuroxime axetil** ester in accordance with the invention is preferably essentially free from crystalline material.

SUMM **Cefuroxime axetil** possesses an asymmetric carbon atom at the 1-position of the 1-acetoxyethyl group and can therefore exist in the form of R and S isomers and mixtures thereof. The amorphous **cefuroxime axetil** ester according to the invention is preferably in the form of a mixture of its R and S isomers, such. . .

SUMM The **cefuroxime axetil** of the invention desirably has an E1cm.sub.1cm.sup.1% at its .lambda..sub.max in methanol, when corrected for any solvent content, of from about 395 to 415. In addition, the **cefuroxime axetil** of the invention having an R to S isomer ratio of from 0.9:1 to 1.1:1, particularly of about 1:1 desirably. . . 1 and 2 of the accompanying drawings are respectively infra-red and n.m.r. spectra for specimens of highly pure, substantially amorphous **cefuroxime axetil** in accordance with the invention.

SUMM After absorption **cefuroxime axetil** is converted into the parent antibiotic acid cefuroxime which is known to exhibit high antibacterial activity against a broad range of gram-positive and gram-negative organisms. **Cefuroxime axetil** is thus

useful in the oral or rectal treatment of a variety of diseases or infections caused by pathogenic bacteria.

SUMM The **cefuroxime axetil** according to the invention is conveniently prepared by a process which constitutes a further feature of the present invention and which comprises recovering **cefuroxime axetil** from a solution thereof under conditions whereby a highly pure, substantially amorphous product is obtained.

SUMM Techniques which may be employed to recover substantially amorphous **cefuroxime axetil** from the solution thereof include those wherein solvent is removed from the solution, preferably rapidly, and the product deposited and. . . wherein the product is precipitated from solution. Methods involving the use of these procedures which have been found satisfactory include **spray drying**, roller drying, solvent precipitation and freeze drying.

SUMM Solvents for **cefuroxime axetil** will be chosen according to the technique and conditions to be employed. Suitable solvents for dissolving **cefuroxime axetil** to form solutions from which recovery is enabled include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM The concentration of **cefuroxime axetil** in the solvent is with advantage as high as possible, commensurate with a substantially amorphous product being obtained, preferred concentrations being greater than 1% m/m, preferably greater than 10% m/m. The maximum concentration of the **cefuroxime axetil** in the solvent will depend upon the solvent used and in general will be less than 30% m/m. For example, the concentration of **cefuroxime axetil** in **acetone** will conveniently lie within the range 10 to 20% m/m. The solvents may if desired be heated as an aid. .

.

SUMM In general, we have found that the **cefuroxime axetil** has sufficient heat stability to withstand **spray drying** and accordingly **spray drying** is a preferred method of effecting recovery. **Spray drying** systems can be operated in known manner to obtain an amorphous product essentially free from crystalline material and free from particulate contaminants. Closed cycle **spray drying** systems in which the drying medium is recycled are particularly safe and economic for use in obtaining the product of. . .

SUMM When employing **spray drying**, suitable solvents for dissolving **cefuroxime axetil** prior to **spray drying** include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; esters, e.g. methyl. . .

SUMM . . . inert gases such as nitrogen, argon and carbon dioxide being preferred in this case. The gas inlet temperature to the **spray dryer** will be chosen according to the solvent used, but may for example be in the range 50-140.degree. C. preferably 60-125.degree.. .

.

SUMM The use of rapid evaporation techniques, in particular the use of **spray drying** also leads particularly readily to the formation, under appropriate conditions, of products having a consistent range of particle sizes. The product from **spray drying** has the form of hollow microspheres which can conveniently be compounded into pharmaceutical compositions.

SUMM When employing roller drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM When employing solvent precipitation, suitable solvents from which the **cefuroxime axetil** may be precipitated include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired

in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . . this gives a homogeneous phase. Precipitation may be effected by the addition of appropriate quantities of a non-solvent for the **cefuroxime axetil** . Suitable non-solvents include water, alkanes and mixtures of alkanes, e.g. hexane or medium boiling range petrol (e.g. 60-80.degree. C.), ethers,. . . at least partially miscible and preferably fully miscible. Typical combinations of solvent and non-solvent are dichloromethane/isopropyl ether, ethyl acetate/petrol and **acetone**/water. The solid should be removed from solution as quickly as possible and dried as quickly as possible to avoid formation. . .

SUMM . . . technique of solvent precipitation may usefully be applied to the reaction mixture remaining after an esterification reaction in which the **cefuroxime axetil** has been formed in order to obtain amorphous **cefuroxime axetil** directly. This may be achieved by the addition of a solvent e.g. an ester such as ethyl acetate to the. . .

SUMM When employing freeze-drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include dioxan and t-butanol. The temperature at which the recovery will be effected will depend upon the. . .

SUMM In order to obtain **cefuroxime axetil** ester in highly pure form by the above techniques it is necessary to employ a starting material of suitable purity--i.e.. . .

SUMM The solution from which the **cefuroxime axetil** is recovered preferably contains a mixture of both R- and S- isomers, whereby the product is obtained as a mixture. . . general, the R/S isomer ratio of the product in solution is exactly reflected in the final product obtained e.g. by **spray drying**, and this ratio for the final product can accordingly be controlled if desired by adjustment of the R/S isomer ratio. . .

SUMM The **cefuroxime axetil** ester according to the invention may be formulated for oral (including buccal) or rectal administration.

SUMM . . . Such pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable **excipients** such as binding agents e.g. pregelatinised maize starch, polyvinyl-pyrrolidone or hydroxypropyl-**methylcellulose**; fillers e.g. starch, **lactose**, micro-crystalline **cellulose** or calcium phosphates; lubricants e.g. magnesium **stearate**, hydrogenated vegetable oils, talc, silica, polyethyleneglycols; disintegrants e.g. potato starch or sodium **starch glycolate**; or wetting agents e.g. sodium lauryl sulphate. Flow aids e.g. silicon dioxide may also be used if desired. The tablets. . .

SUMM The preparation of a composition suitable for forming into tablets, capsules or granules may also be achieved by **spray-drying** or roller drying a suspension of pure amorphous **cefuroxime axetil** with the **excipients** appropriate for the said tablets, capsules or granules.

SUMM . . . liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents e.g. sorbitol syrup, methyl **cellulose** or hydrogenated edible fats and oils such as hydrogenated castor oil; emulsifying or thickening agents e.g. lecithin, aluminium **stearates** or acacia; non-aqueous vehicles e.g. almond oil, fractionated coconut oil, oily esters or ethyl alcohol; and preservatives e.g. methyl or. . .

SUMM The **cefuroxime axetil** of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository. . .

SUMM In a further aspect therefore the invention provides a pharmaceutical composition comprising **cefuroxime axetil** in highly pure, substantially amorphous form, in admixture with one or more pharmaceutical carriers and/or **excipients**. Such compositions are preferably adapted for absorption via the gastrointestinal tract,

e.g. for oral administration. In a preferred embodiment, such. . .

SUMM . . . comprises administering to the said body orally or rectally an effective amount of a highly pure, substantially amorphous form of **cefuroxime axetil**.

SUMM The following non-limiting Examples illustrate the invention. In all these Examples, the **cefuroxime axetil** starting materials used were in highly pure crystalline form. Such starting materials may for example be obtained by processes as described in British Patent No. 1571683, or may alternatively be prepared by the crystallisation of highly pure **cefuroxime axetil** from an organic solvent, for example an ester such as ethyl acetate in admixture with an ether such as isopropyl. . .

SUMM . . . by hydrolysis in situ at a temperature of +10.degree. to +30.degree. C. and crystallisation by addition of sodium 2-ethylhexanoate in **acetone** or methyl acetate as solvent.

SUMM Crystalline **Cefuroxime Axetil**

SUMM . . . washed with 2:1 diisopropyl ether/ethyl acetate (150 ml) and dried for a weekend in vacuo at 50.degree. to give crystalline **cefuroxime axetil** (19.3 g).

DETD A 10% m/v **acetone** solution of a mixture of R and S isomers of **cefuroxime axetil** was put through a Niro Mobile Minor **Spray Drier**, supplied by Niro Copenhagen, Denmark, using air as the drying gas and a rotary atomizer running at about 35,000 rpm. The gas inlet and outlet temperatures were 124.degree. and 70.degree. respectively. A recovery of 75% m/m of **spray dried** product was obtained. The microscopic appearance was typical for a **spray dried** product (hollow spheres). Assay by HPLC was 97% m/m and impurities by HPLC 2.0% m/m, both calculated to dry from. . .

DETD A mixture of R and S isomers of **cefuroxime axetil** (20.25 g) was dissolved in **acetone** (200 ml) at ambient temperature. The solution was clarified through sintered glass and pumped through a two fluid atomizer jet, using nitrogen under 1 kg/cm.sup.2 as the atomising fluid, into the glass drying chamber of a Mini Spray HO **spray drying** apparatus using an approximately 50:50 mixture of air and nitrogen as the drying gas. The gas inlet and outlet temperatures were 75.degree. and 55.degree. respectively. The recovery was 14.1 g (70.5%) of amorphous material containing 1.1% m/m **acetone** (GLC). Impurities (by HPLC) 1.7% m/m including 0.2% m/m ceph-2-em compound. Isomer ratio 1.03:1. .nu..sub.max (Nujol) similar to that shown. . .

DETD A 15% **acetone** solution of **cefuroxime axetil** (ca 1:1 mixture of R and S isomers) was put through a closed cycle **spray dryer** using nitrogen as the recycling gas and a rotating wheel atomiser running at 24,000 rpm. The gas inlet and outlet temperatures were 105.degree. and 70.degree. respectively. The recycling gas was cooled to remove most of the evaporated **acetone**. Recovery of amorphous product was 90% with an **acetone** content of 1.0% m/m (GLC), water 0.7% m/m (Karl Fischer), HPLC impurity level 1.3% m/m. Infrared (Nujol) (KBr plates) and. . .

DETD Further Examples 4 to 17 illustrating the preparation of amorphous **cefuroxime axetil** are given in the following Table. The process of these examples was similar to that of Example 2. The Nujol. . .

DETD

Ex No.	Solvent	Inlet Temp .degree.C.	Outlet Temp .degree.C.
4.	**Acetone**/water	62	55
5.	Industrial methylated spirit	80	70
6.	Acetonitrile	72	63
7.	Tetrahydrofuran	75	65

8.	Methylacetate	63	55
9.	Chloroform (water set)	64	58
10.	**Acetone**/water	70	50
11.	Ethylacetate/water	72	64
12.	Methylacetate/water	64	57
13.	Methanol/water	67-70	55-59
14.	Methanol/**acetone**	63	54
15.	Ethanol/**acetone**	83	65
16.	**Acetone**/methylacetate	63	54
17.	**Acetone**	85-90	75

Ex No.	Product Isomer Ratio	Impurities (% m/m)	[.alpha.].sub.D (dioxan)	E.sub.1 cm.sup.1% (MeOH)
4.	1.05:1	1.8	+35.degree.	390

5.. . .

DETD A solution of purified crystalline cefuroxime 1-acetoxyethyl ester (isomer A) (77 g) in **acetone** (1.8 liters) at 45.degree. was **spray dried** as in Example 2 through a two fluid atomizer nozzle with a nitrogen atomizing pressure of 0.5 kg/cm.sup.2. The gas inlet temperature was 85-90.degree. and the outlet temperature ca 75.degree.. The product (39 g) had an **acetone** content of 0.15% m/m and impurities by HPLC of 2.8% m/m. The infrared spectrum (Nujol) confirmed the amorphous nature of. . .

DETD A mixture of the R and S isomers of **cefuroxime axetil** (10 g) was dissolved in hot **acetone** (70 ml) and evaporated in vacuo to a froth. This was broken up and dried overnight in vacuo at 40.degree. to give 9.8 g of **cefuroxime axetil** which was shown by IR (Nujol) (which was similar to that in FIG. 1) and microscopic examination to be amorphous. The **acetone** content (GLC) was 2.9%. Impurities by HPLC were 3.4% m/m and the isomer ratio was 1.14:1.

DETD Following the above procedure, pure amorphous **cefuroxime axetil** was also obtained using IMS, methanol and ethyl acetate as solvents.

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (5 g) was dissolved in boiling ethylacetate (200 ml) and concentrated at atmospheric pressure to 70 ml. The solution was. . . displacement washed with petroleum ether (bp. 60.degree.-80.degree.) and dried overnight in vacuo at 50.degree. to give 4.5 g of amorphous **cefuroxime axetil**. Solvent content (GLC) 0.25% m/m; [.alpha.].sub.D (1% in dioxan) +39.degree.; E.sub.1cm.sup.1% (MeOH) 388. Microscopic examination confirmed the amorphous nature of. . .

DETD A ca 1:1 mixture of the R and S isomers of **Cefuroxime axetil** (6 g) was dissolved in boiling dichloromethane (240 ml), allowed to cool and filtered. The filtrate was distilled to a. . . filtered, washed with di-isopropyl ether (100 ml) and dried overnight in vacuo at 50.degree. to give 5.5 g of amorphous **cefuroxime axetil**. Microscopic examination suggested <1% crystalline material. [.alpha.].sub.D (1% dioxan) +36.degree., E.sub.1cm.sup.1% 387 (MeOH). Solvent content (GLC), 1%.

DETD . . . nitrogen was bubbled in at 12 l min.sup.-1. A solution of a mixture of the R and S isomers of **cefuroxime axetil** (200 g) dissolved in a warm (45.degree.) mixture of **acetone** (600 ml) and water (66 ml) was then added with the aid of a peristaltic pump at a constant rate over 13 minutes into the vortex of the water. The precipitated amorphous **cefuroxime axetil** was carried through the horizontal aperture as a froth and collected. The

amorphous **cefuroxime axetil** product was harvested immediately and dried to constant weight in vacuo at 55.degree. to yield 170 g. Solvent content (GLC)<0.01. . .

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (100 g) was dissolved by stirring in **acetone** (1 l) and warming to 40.degree.. The rollers of a drier were heated to 75.degree., steam (two bar pressure) was. . . jacket and 737 mm vacuum applied to the apparatus. Using a roller speed of 1.75 rpm the prepared solution of **cefuroxime axetil** was sucked in at a rate of ca 200 ml/min. The product was knifed from the rollers and collected in. . .

DETD A solution of a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (10 g) in dioxan (100 ml) was freeze dried to give the product (10.7 g) which contained dioxan 5.5% m/m. . .

DETD . . . of petrol (105 ml) and ethyl acetate (12 ml) followed by petrol (118 ml). Drying at 40.degree. in vacuo gave **cefuroxime axetil** 17.9 g: Solvents (GLC), ethylacetate 1.6%, petrol 1.5%; impurities by HPLC 4.1% m/m, isomer ratio 1.06:1; E.sub.1cm.sup.1% (MeOH) 364. The. . .

DETD **Acetone** (2000 ml), water (324 ml) and IMS (36 ml) were added to a stirred flask followed by a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (600 g). The contents of the flask were heated to 42.degree. and stirred until the solid dissolved. Immediately prior to. . .

DETD Water (850 ml/min) and the **cefuroxime axetil** solution (115 ml/min) was added simultaneously into the turbulent zone in the precipitator. The overflow from the precipitator was directed. . .

DETD . . . dried in vacuo at 45.degree. until the moisture content was reduced to less than 1% to yield 410 g of **cefuroxime axetil**.

DETD

Pharmacy Examples

1. Tablet

Composition	mg/tablet
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Starch 1500 (Colorcon, Inc) (Pregelatinised starch)	161.5
Sodium **Starch Glycolate**	20.0
Sodium Lauryl Sulphate	10.0
Polyethylene glycol 6000 (micronized)	7.5
Silicon Dioxide	1.0
Total weight	500.0

DETD The polyethylene glycol, sodium lauryl sulphate, sodium **starch glycolate** and silicon dioxide were passed through a 60 mesh screen and blended with a small quantity of the active ingredient.. . .

DETD The tablet may then be film coated with **cellulose** derivatives with plasticisers, colouring agents and preservatives if necessary, using aqueous or organic solvent methods.

DETD

2. Capsule

Composition	mg/capsule
Cefuroxime axetil according to the invention	300.00 (equivalent

to the invention to 250 mg cefuroxime)
Microcrystalline **cellulose**
24.75
Hydrogenated Vegetable Oil
4.0
Sodium Lauryl Sulphate
9.0
Silicon Dioxide 1.25

DETD
3. Powder for oral suspension (in sachet)
Composition (per sachet)

Cefuroxime axetil according to the invention	300	mg
Sodium lauryl sulphate	25	mg
Hydroxypropyl-methyl-**cellulose**	90	mg
Spray dried orange flavour	150	mg
Castor sugar to	2220	mg

DETD The sodium lauryl sulphate, hydroxypropyl-methyl-**cellulose** and flavour were triturated with the active ingredient. This blend was then further blended with castor sugar, adding the latter. . .

DETD
4. Oily Suspension
Composition (per 5 ml dose)

Cefuroxime axetil according to the invention	300	mg
Lecithin	35	mg
Butylhydroxybenzoate	2	mg
Aluminium monostearate	25	mg
Aluminium distearate	25	mg
Hydrogenated castor oil	17.5	mg

Liquid flavour. . .

DETD Some of the coconut oil was heated, then the lecithin, butylhydroxybenzoate aluminium **stearates**, hydrogenated castor oil, icing sugar and sodium chloride were added to the oil with mixing.

DETD The mixture was cooled and the **cefuroxime axetil** and flavour added. The remainder of the required coconut oil was then added and the preparation was mixed and refined.

CLM What is claimed is:

1. A process for the preparation of highly pure **cefuroxime axetil** in predominantly amorphous form which comprises recovering **cefuroxime axetil** from a solution thereof by roller drying.

3. The process of claim 1 wherein the concentration of **cefuroxime axetil** in the solution prior to recovery is at least 1% m/m.

4. The process of claim 1 wherein the concentration of **cefuroxime axetil** in the solution prior to recovery is at least 10% m/m.

5. A process for preparing a highly pure, substantially amorphous form of **cefuroxime axetil** which comprises preparing a highly pure solution of **cefuroxime axetil** and roller drying said solution to recover highly pure, substantially amorphous **cefuroxime axetil**.

7. The process of claim 5 wherein the concentration of

cefuroxime axetil in the solution prior to recovery is at least 1% m/m.

8. The process of claim 5 wherein the concentration of **cefuroxime axetil** in the solution prior to recovery is at least 10% m/m.

IT 64-17-5, uses and miscellaneous 67-56-1, uses and miscellaneous **67-64-1**, uses and miscellaneous 67-66-3, uses and miscellaneous 75-05-8, uses and miscellaneous 75-09-2, uses and miscellaneous 79-20-9 108-20-3 109-99-9, uses and miscellaneous 123-91-1, uses and miscellaneous 141-78-6, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)

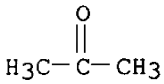
IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)

IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)

IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)

IT **67-64-1**, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)

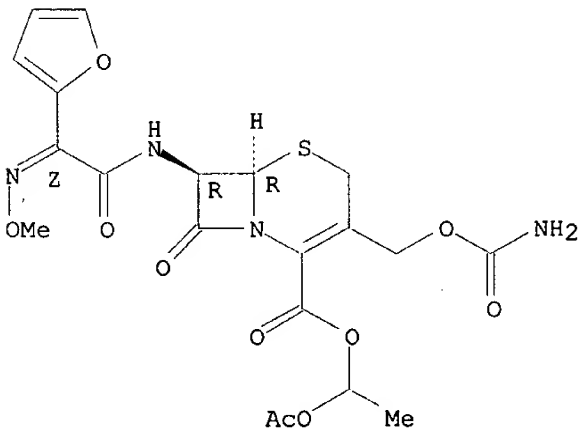
RN 67-64-1 USPATFULL
CN 2-Propanone (9CI) (CA INDEX NAME)



IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)

RN 64544-07-6 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

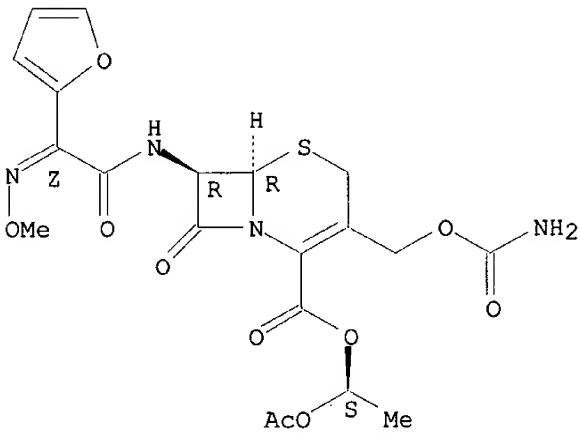


IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)

RN 64599-29-7 USPATFULL

CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1S)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

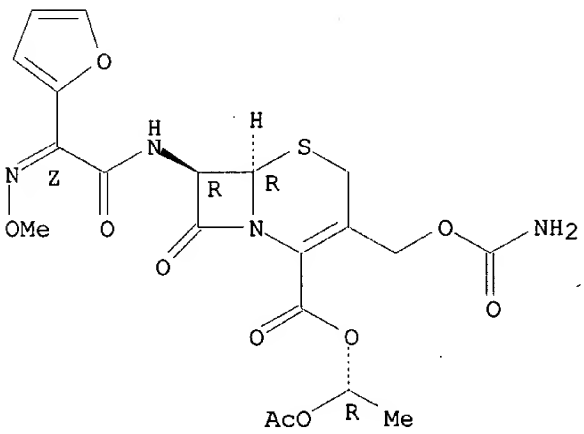


IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)

RN 64599-28-6 USPATFULL

CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1R)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L66 ANSWER 3 OF 5 USPATFULL

AN 89:28035 USPATFULL

TI Preparation of a highly pure, substantially amorphous form of **cefuroxime axetil**

IN Crisp, Harold A., Harrow Weald, England
Clayton, John C., Fastcote, England
Elliott, Leonard G., Great Urswick, England
Wilson, Edward M., St. John's Close, England

PA Glaxo Group Limited, London, England (non-U.S. corporation)

PI US 4820833 19890411 <--
AI US 1986-938140 19861204 (6) <--
DCD 20021231
RLI Continuation of Ser. No. US 1985-781505, filed on 30 Sep 1985, now abandoned which is a continuation of Ser. No. US 1985-711559, filed on 14 Mar 1985, now abandoned which is a continuation of Ser. No. US 1984-635797, filed on 30 Jul 1984, now abandoned which is a continuation of Ser. No. US 1983-518671, filed on 29 Jul 1983, now abandoned
PRAI GB 1982-22019 19820730 <--
DT Utility
EXNAM Primary Examiner: Daus, Donald G.; Assistant Examiner: Noel, Mark W.
LREP Bacon & Thomas
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 698
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level of bioavailability on oral or rectal administration.

Methods of preparing the product are also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.

Also disclosed are pharmaceutical compositions containing the product and methods for its use in medicine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Preparation of a highly pure, substantially amorphous form of **cefuroxime axetil**
PI US 4820833 19890411 <--
AI US 1986-938140 19861204 (6) <--
PRAI GB 1982-22019 19820730 <--
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level. . .
AB . . . also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.
SUMM This invention relates to a novel, amorphos form of the 1-acetoxyethyl ester of cefuroxime(**cefuroxime axetil**), to a process for the preparation thereof, to a composition containing it and to its use in medicine.
SUMM Of the esters described in British Patent Specification No. 1571683, we have found **cefuroxime axetil** to be of particular interest. The processes for the preparation of the above ester exemplified in British Patent Specification No.. . .
SUMM In view of past experience in the cephalosporin field, we first prepared **cefuroxime axetil** for commercial evaluation in substantially pure, crystalline form. We have however surprisingly found that substantially pure, crystalline **cefuroxime axetil** does not have the best balance of properties for commercial use and that, contrary to previous experience in the cephalosporin field, **cefuroxime axetil** is advantageously used in a highly pure, substantially amorphous form. We have thus established that highly pure **cefuroxime axetil** when in substantially amorphous form has higher bioavailability upon oral administration than when in crystalline form and that moreover the amorphous form of **cefuroxime axetil** has adequate chemical stability upon

storage. This is despite the known tendency for amorphous materials to have inferior chemical stability. . . known tendency for highly pure amorphous materials to crystallise. Thus, unlike previous cephalosporin compounds which have been developed for commercialisation, **cefuroxime axetil** is advantageously prepared and used in highly pure amorphous form rather than in crystalline form.

SUMM According to one aspect of the present invention, there is provided **cefuroxime axetil** in highly pure, substantially amorphous form.

SUMM The **cefuroxime axetil** in accordance with the invention preferably contains less than 5% mass/mass (m/m), advantageously less than 3% m/m, of impurities. It. . . `impurities` are to be understood as not including residual solvents remaining from the process used in the preparation of the **cefuroxime axetil** of the invention. Any residual solvent present will desirably only be present in less than 6% m/m and most preferably. . .

SUMM Typical impurities which may be present are the .DELTA..sup.2 -isomers of **cefuroxime axetil** and the corresponding E-isomers of **cefuroxime axetil**.

SUMM The **cefuroxime axetil** ester in accordance with the invention is preferably essentially free from crystalline material.

SUMM **Cefuroxime axetil** possesses an asymmetric carbon atom at the 1-position of the 1-acetoxyethyl group and can therefore exist in the form of R and S isomers and mixtures thereof. The amorphous **cefuroxime axetil** ester according to the invention is preferably in the form of a mixture of its R and S isomers, such. . .

SUMM The **cefuroxime axetil** of the invention desirably has an E.sub.1cm.sup.1% at its .lambda..sub.max in methanol, when corrected for any solvent content, of from about 395 to 415. In addition, the **cefuroxime axetil** of the invention having an R to S isomer ratio of from 0.9:1 to 1.1:1, particularly of about 1:1 desirably. . . 1 and 2 of the accompanying drawings are respectively infra-red and n.m.r. spectra for specimens of highly pure, substantially amorphous **cefuroxime axetil** in accordance with the invention.

SUMM After absorption **cefuroxime axetil** is converted into the parent antibiotic acid cefuroxide which is known to exhibit high antibacterial activity against a broad range of gram-positive and gram-negative organisms. **Cefuroxime axetil** is thus useful in the oral or rectal treatment of a variety of diseases or infections caused by pathogenic bacteria.

SUMM The **cefuroxime axetil** according to the invention is conveniently prepared by a process which constitutes a further feature of the present invention and which comprises recovering **cefuroxime axetil** from a solution thereof under conditions whereby a highly pure, substantially amorphous product is obtained.

SUMM Techniques which may be employed to recover substantially amorphous **cefuroxime axetil** from the solution thereof include those wherein solvent is removed from the solution, preferably rapidly, and the product deposited and. . . wherein the product is precipitated from solution. Methods involving the use of these procedures which have been found satisfactory include **spray drying**, roller drying, solvent precipitation and freeze drying.

SUMM Solvents for **cefuroxime axetil** will be chosen according to the technique and conditions to be employed. Suitable solvents for dissolving **cefuroxime axetil** to form solutions from which recovery is enabled include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM The concentration of **cefuroxime axetil** in the solvent is with advantage as high as possible, commensurate with a substantially amorphous product being obtained, preferred concentrations being greater than 1% m/m, preferably greater than 10% m/m. The maximum concentration of the **cefuroxime axetil** in the

solvent will depend upon the solvent used and in general will be less than 30% m/m. For example, the concentration of **cefuroxime axetil** in **acetone** will conveniently lie within the range 10 to 20% m/m. The solvents may if desired be heated as an aid. . .

SUMM In general, we have found that the **cefuroxime axetil** has sufficient heat stability to withstand **spray drying** and accordingly **spray drying** is a preferred method of effecting recovery. **Spray drying** systems can be operated in known manner to obtain an amorphous product essentially free from crystalline material and free from particulate contaminants. Closed cycle **spray drying** systems in which the drying medium is recycled are particularly safe and economic for use in obtaining the product of. . .

SUMM When employing **spray drying**, suitable solvents for dissolving **cefuroxime axetil** prior to **spray drying** include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; esters, e.g. methyl. . .

SUMM . . . inert gases such as nitrogen, argon and carbon dioxide being preferred in this case. The gas inlet temperature to the **spray dryer** will be chosen according to the solvent used, but may for example be in the range 50.degree.-140.degree. C. preferably 60.degree.-125.degree.. . .

SUMM The use of rapid evaporation techniques, in particular the use of **spray drying** also leads particularly readily to the formation, under appropriate conditions, of products having a consistent range of particle sizes. The product from **spray drying** has the form of hollow microspheres which can conveniently be compounded into pharmaceutical compositions.

SUMM When employing roller drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM When employing solvent precipitation, suitable solvents from which the **cefuroxime axetil** may be precipitated include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . . this gives a homogeneous phase. Precipitation may be effected by the addition of appropriate quantities of a non-solvent for the **cefuroxime axetil** . Suitable non-solvents include water, alkanes and mixtures of alkanes, e.g. hexane or medium boiling range petrol (e.g. 60.degree.-80.degree. C.), ethers,. . . at least partially miscible and preferably fully miscible. Typical combinations of solvent and non-solvent are dichloromethane/isopropyl ether, ethyl acetate/petrol and **acetone**/water. The solid should be removed from solution as quickly as possible and dried as quickly as possible to avoid formation. . .

SUMM . . . technique of solvent precipitation may usefully be applied to the reaction mixture remaining after an esterification reaction in which the **cefuroxime axetil** has been formed in order to obtain amorphous **cefuroxime axetil** directly. This may be achieved by the addition of a solvent e.g. an ester such as ethyl acetate to the. . .

SUMM When employing freeze-drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include dioxan and t-butanol. The temperature at which the recovery will be effected will depend upon the. . .

SUMM In order to obtain **cefuroxime axetil** ester in highly pure form by the above techniques it is necessary to employ a starting material of suitable purity. . .

SUMM The solution from which the **cefuroxime axetil** is recovered preferably contains a mixture of both R- and S- isomers,

whereby the product is obtained as a mixture. . . general, the R/S isomer ratio of the product in solution is exactly reflected in the final product obtained e.g. by **spray drying**, and this ratio for the final product can accordingly be controlled if desired by adjustment of the R/S isomer ratio. . .

SUMM The **cefuroxime axetil** ester according to the invention may be formulated for oral (including buccal) or rectal administration.

SUMM . . . Such pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable **excipients** such as binding agents e.g. pregelatinised maize starch, polyvinyl-pyrrolidone or hydroxypropyl-**methylcellulose**; fillers e.g. starch, **lactose**, micro-crystalline **cellulose** or calcium phosphates; lubricants e.g. magnesium **stearate**, hydrogenated vegetable oils, talc, silica, polyethyleneglycols; disintegrants e.g. potato starch or sodium **starch glycolate**; or wetting agents e.g. sodium lauryl sulphate. Flow aids e.g. silicon dioxide may also be used if desired. The tablets. . .

SUMM The preparation of a composition suitable for forming into tablets, capsules or granules may also be achieved by **spray-drying** or roller drying a suspension of pure amorphous **cefuroxime axetil** with the **excipients** appropriate for the said tablets, capsules or granules.

SUMM . . . liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents e.g. sorbitol syrup, methyl **cellulose** or hydrogenated edible fats and oils such as hydrogenated castor oil; emulsifying or thickening agents e.g. lecithin, aluminium **stearates** or acacia; non-aqueous vehicles e.g. almond oil, fractionated coconut oil, oily esters or ethyl alcohol; and preservatives e.g. methyl or. . .

SUMM The **cefuroxime axetil** of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository. . .

SUMM In a further aspect therefore the invention provides a pharmaceutical composition comprising **cefuroxime axetil** in highly pure, substantially amorphous form, in admixture with one or more pharmaceutical carriers and/or **excipients**. Such compositions are preferably adapted for absorption via the gastrointestinal tract, e.g. for oral administration. In a preferred embodiment, such. . .

SUMM . . . comprises administering to the said body orally or rectally an effective amount of a highly pure, substantially amorphous form of **cefuroxime axetil**.

SUMM The following non-limiting Examples illustrate the invention. In all these Examples, the **cefuroxime axetil** starting materials used were in highly pure crystalline form. Such starting materials may for example be obtained by processes as described in British patent No. 1571683, or may alternatively be prepared by the crystallisation of highly pure **cefuroxime axetil** from an organic solvent, for example an ester such as ethyl acetate in admixture with an ether such as isopropyl. . .

SUMM . . . by hydrolysis in situ at a temperature of +10.degree. to +30.degree. C. and crystallisation by addition of sodium 2-ethylhexanoate in **acetone** or methyl acetate as solvent.

DETD Crystalline **Cefuroxime Axetil**

DETD . . . washed with 2:1 diisopropyl ether/ethyl acetate (150 ml) and dried for a weekend in vacuo at 50.degree. to give crystalline **cefuroxime axetil** (19.3 g).

DETD A 10% m/v **acetone** solution of a mixture of R and S isomers of **cefuroxime axetil** was put through a Niro Mobile Minor **Spray Drier**, supplied by Niro Copenhagen, Denmark, using air as the drying gas and a rotary atomizer running at about 35,000 rpm. The gas inlet and outlet temperatures were 124.degree. and 70.degree. respectively. A recovery of 75% m/m of **spray dried** product was obtained. The microscopic appearance was typical for a **spray dried** product (hollow spheres).

Assay by HPLC was 97% m/m and impurities by HPLC 2.0% m/m, both calculated to dry from. . .

DETD A mixture of R and S isomers of **cefuroxime axetil** (20.25 g) was dissolved in **acetone** (200 ml) at ambient temperature. The solution was clarified through sintered glass and pumped through a two fluid atomizer jet, using nitrogen under 1 kg/cm.sup.2 as the atomising fluid, into the glass drying chamber of a Mini Spray HO **spray drying** apparatus using an approximately 50:50 mixture of air and nitrogen as the drying gas. The gas inlet and outlet temperatures were 75.degree. and 55.degree. respectively. The recovery was 14.1 g (70.5%) of amorphous material containing 1.1% m/m **acetone** (GLC). Impurities (by HPLC) 1.7% m/m including 0.2% m/m ceph-2-em compound. Isomer ratio 1.03:1. .nu..sub.max (Nujol) similar to that shown. . .

DETD A 15% **acetone** solution of **cefuroxime axetil** (ca 1:1 mixture of R and S isomers) was put through a closed cycle **spray dryer** using nitrogen as the recycling gas and a rotating wheel atomiser running at 24,000 rpm. The gas inlet and outlet temperatures were 105.degree. and 70.degree. respectively. The recycling gas was cooled to remove most of the evaporated **acetone**. Recovery of amorphous product was 90% with an **acetone** content of 1.0% m/m (GLC), water 0.7% m/m (Karl Fischer), HPLC impurity level 1.3% m/m. Infrared (Nujol) (KBr plates) and. . .

DETD Further Examples 4 to 17 illustrating the preparation of amorphous **cefuroxime axetil** are given in the following Table. The process of these examples was similar to that of Example 2. The Nujol. . .

DETD . . . Inlet Temp | Outlet Temp | Product Isomer Ratio (% m/m) (dioxan) (MeOH) | Impurities [.alpha.].sub.D E.sup.1% .sub.1 cm

Ex No. Solvent	Inlet Temp .degree.C.	Outlet Temp .degree.C.	Product Isomer Ratio (% m/m) (dioxan) (MeOH)	Impurities	[.alpha.].sub.D E.sup.1% .sub.1 cm
4. **Acetone**/water	62	55	1.05:1	1.8	+35.degree. 390
5. Industrial methylated spirit	80	70	1.05:1	1.9	+36.degree. 386
6. Acetonitrile	72	63	1.00:1	1.6. . .	75 65 1.04:1
				2.0	+34.degree. 384
8. Methylacetate	63	55	0.94:1	1.3	+35.degree. 387
9. Chloroform (water set)	64	58	1.02:1	1.5	
10. **Acetone**/water					

70 50 1.05:1
1.2
11. Ethylacetate/water
72 64 1.02:1
1.4
12. Methylacetate/water
64 57 0.98:1
1.2
13. Methanol/water
67-70
55-59
1.04:1
1.9
14. Methanol/**acetone**
63 54 1.03:1
1.4
15. Ethanol/**acetone**
83 65 1.02:1
1.6
16. **Acetone**/methylacetate
63 54 1.02:1
1.6
17. **Acetone** 85-90
75 pure B
0.9 +9.degree.
387

DETD A solution of purified crystalline cefuroxime 1-acetoxyethyl ester (isomer A) (77 g) in **acetone** (1.8 litres) at 45.degree. was **spray dried** as in Example 2 through a two fluid atomizer nozzle with a nitrogen atomizing pressure of 0.5 kg/cm.sup.2. The gas inlet temperature was 85.degree.-90.degree. and the outlet temperature ca 75.degree. . The product (39 g) had an **acetone** content of 0.15% m/m and impurities by HPLC of 2.8% m/m. The infrared spectrum (Nujol) confirmed the amorphous nature of. . .

DETD A mixture of the R and S isomers of **cefuroxime axetil** (10 g) was dissolved in hot **acetone** (70 ml) and evaporated in vacuo to a froth. This was broken up and dried overnight in vacuo at 40.degree. to give 9.8 g of **cefuroxime axetil** which was shown by IR (Nujol) (which was similar to that in FIG. 1) and microscopic examination to be amorphous. The **acetone** content (GLC) was 2.9%. Impurities by HPLC were 3.4% m/m and the isomer ratio was 1.14:1.

DETD Following the above procedure, pure amorphous **cefuroxime axetil** was also obtained using IMS, methanol and ethyl acetate as solvents.

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (5 g) was dissolved in boiling ethylacetate (200 ml) and concentrated at atmospheric pressure to 70 ml. The solution was. . . displacement washed with petroleum ether (bp. 60.degree.-80.degree.) and dried overnight in vacuo at 50.degree. to give 4.5 g of amorphous **cefuroxime axetil**. Solvent content (GLC) 0.25% m/m; [.alpha.].sub.D (1% in dioxan) +39.degree. ; E.sub.1cm.sup.1% (MeOH) 388. Microscopic examination confirmed the amorphous nature. . .

DETD A ca 1:1 mixture of the R and S isomers of **Cefuroxime axetil** (6 g) was dissolved in boiling dichloromethane (240 ml), allowed to cool and filtered. The filtrate was distilled to a. . . filtered, washed with di-isopropyl ether (100 ml) and dried overnight in vacuo at 50.degree. to give 5.5 g of amorphous **cefuroxime axetil**. Microscopic examination suggested <1% crystalline material. [.alpha.].sub.D (1% dioxan) +36.degree., E.sub.1cm.sup.1% 387 (MeOH). Solvent content (GLC), 1%.

DETD . . . nitrogen was bubbled in at 12 1 min.sup.-1. A solution of a mixture of the R and S isomers of **cefuroxime axetil** (200 g) dissolved in a warm (45.degree.) mixture of **acetone** (600 ml) and water (66 ml) was then added with the aid of a peristaltic

pump at a constant rate over 13 minutes into the vortex of the water. The precipitated amorphous **cefuroxime axetil** was carried through the horizontal aperture as a froth and collected. The amorphous **cefuroxime axetil** product was harvested immediately and dried to constant weight in vacuo at 55.degree. to yield 170 g. Solvent content (GLC)<0.01. . .

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (100 g) was dissolved by stirring in **acetone** (1 1) and warming to 40.degree.. The rollers of a drier were heated to 75.degree. , steam (two bar pressure). . . jacket and 737 mm vacuum applied to the apparatus. Using a roller speed of 1.75 rpm the prepared solution of **cefuroxime axetil** was sucked in at a rate of ca 200 ml/min. The product was knifed from the rollers and collected in. . .

DETD A solution of a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (10 g) in dioxan (100 ml) was freeze dried to give the product (10.7 g) which contained dioxan 5.5% m/m. .

DETD . . . of petrol (105 ml) and ethyl acetate (12 ml) followed by petrol (118 ml). Drying at 40.degree. in vacuo gave **cefuroxime axetil** 17.9 g: Solvents (GLC), ethylacetate 1.6%, petrol 1.5%; impurities by HPLC 4.1% m/m, isomer ratio 1.06:1; E.sub.1cm.sup.1% (MeOH) 364. The. . .

DETD **Acetone** (2000 ml), water (324 ml) and IMS (36 ml) were added to a stirred flask followed by a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (600 g). The contents of the flask were heated to 42.degree. and stirred until the solid dissolved. Immediately prior to. . .

DETD Water (850 ml/min) and the **cefuroxime axetil** solution (115 ml/min) was added simultaneously into the turbulent zone in the precipitator. The overflow from the precipitator was directed. .

DETD . . . dried in vacuo at 45.degree. until the moisture content was reduced to less than 1% to yield 410 g of **cefuroxime axetil.**

DETD

1. Tablet

Composition	mg/tablet
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Starch 1500 (Colorcon, Inc) (Pregelatinised starch)	161.5
Sodium **Starch Glycolate**	20.0
Sodium Lauryl Sulphate	10.0
Polyethylene glycol 6000 (micronized)	7.5
Silicon Dioxide	1.0
Total weight	500.0

DETD The polyethylene glycol, sodium lauryl sulphate, sodium **starch glycolate** and silicon dioxide were passed through a 60 mesh screen and blended with a small quantity of the active ingredient.. .

DETD The tablet may then be film coated with **cellulose** derivatives with plasticisers, colouring agents and preservatives if necessary, using aqueous or organic solvent methods.

DETD

2. Capsule

Composition	mg/capsule
Cefuroxime axetil according	

300.00 (equivalent
to the invention to 250 mg cefuroxime)
Microcrystalline **cellulose** 24.75
Hydrogenated Vegetable Oil
4.0
Sodium Lauryl Sulphate
9.0
Silicon Dioxide 1.25

DETD
3. Powder for oral suspension (in sachet)
Composition (per sachet)

Cefuroxime axetil according to the invention	300	mg
Sodium lauryl sulphate	25	mg
Hydroxypropyl-methyl-**cellulose**	90	mg
Spray dried orange flavour	150	mg
Castor sugar to	2220	mg

DETD The sodium lauryl sulphate, hydroxypropylmethyl-**cellulose** and flavour were triturated with the active ingredient. This blend was then further blended with castor sugar, adding the latter. . .

DETD
4. Oily Suspension
Composition (per 5 ml dose)

Cefuroxime axetil according to the invention	300	mg
Lecithin	35	mg
Butylhydroxybenzoate	2	mg
Aluminum monostearate	25	mg
Aluminium distearate	25	mg
Hydrogenated castor oil	17.5	mg

Liquid flavour. . .

DETD Some of the coconut oil was heated, then the lecithin, butylhydroxybenzoate aluminium **stearates**, hydrogenated castor oil, icing sugar, and sodium chloride were added to the oil with mixing.

DETD The mixture was cooled and the **cefuroxime axetil** and flavour added. The remainder of the required coconut oil was then added and the preparation was mixed and refined.

CLM What is claimed is:

1. A process for preparing a highly pure, substantially amorphous form of **cefuroxime axetil** which comprises preparing a highly pure solution of **cefuroxime axetil** and **spray drying** said solution to recover highly pure, substantially amorphous cefuroxine axetil.

3. The process of claim 1 wherein the concentration of **cefuroxime axetil** in the solution prior to recovery is at least 1% m/m.

4. The process of claim 1 wherein the concentration of **cefuroxime axetil** in the solution prior to recovery is at least 10% m/m.

5. The process of claim 1 wherein the **spray drying** is effected in the presence of an inert gas.

IT 64-17-5, uses and miscellaneous 67-56-1, uses and miscellaneous
67-64-1, uses and miscellaneous 67-66-3, uses and miscellaneous
75-05-8, uses and miscellaneous 75-09-2, uses and miscellaneous

79-20-9 108-20-3 109-99-9, uses and miscellaneous 123-91-1, uses and miscellaneous 141-78-6, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)

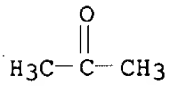
IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)

IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)

IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)

IT **67-64-1**, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)

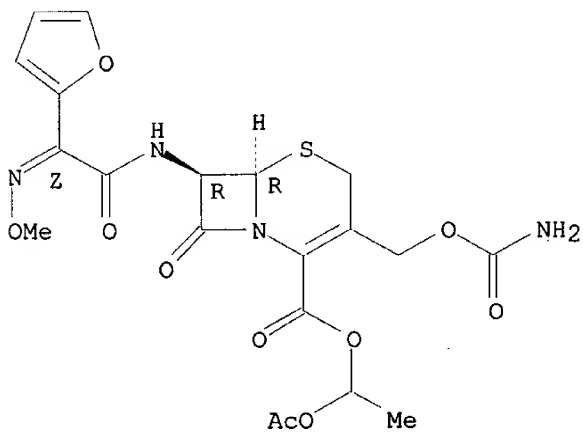
RN 67-64-1 USPATFULL
CN 2-Propanone (9CI) (CA INDEX NAME)



IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)

RN 64544-07-6 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

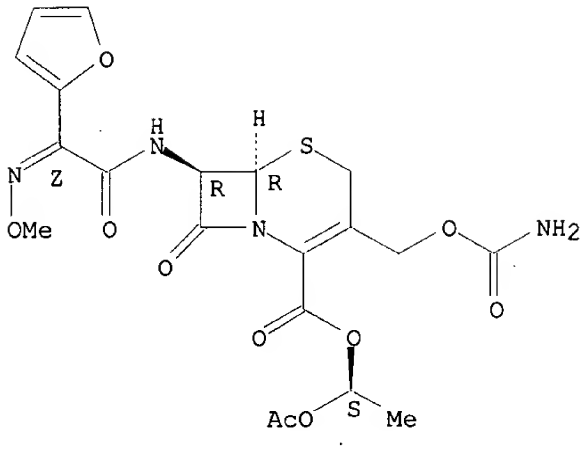
Absolute stereochemistry.
Double bond geometry as shown.



IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)

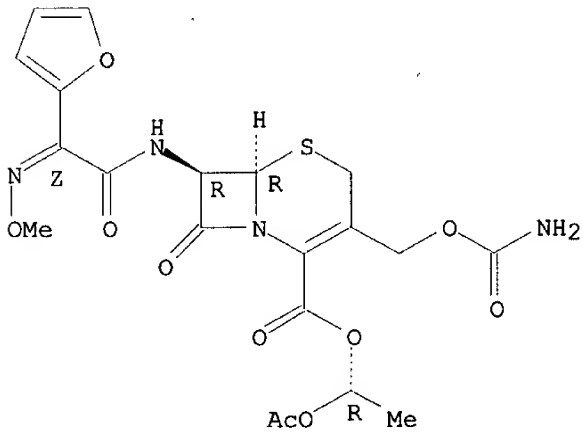
RN 64599-29-7 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1S)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)
RN 64599-28-6 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1R)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L66 ANSWER 4 OF 5 USPATFULL
AN 85:76854 USPATFULL
TI Amorphous form of cefuroxime ester
IN Crisp, Harold A., Harrow Weald, England
Clayton, John C., Pinner, England
PA Glaxo Group Limited, London, England (U.S. corporation)
PI US 4562181 19851231 <--
AI US 1983-518693 19830729 (6) <--
PRAI GB 1982-22019 19820730 <--
DT Utility
EXNAM Primary Examiner: Daus, Donald G.; Assistant Examiner: Benson, Robert
LREP Bacon & Thomas
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 710

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level of bioavailability on oral or rectal administration.

Methods of preparing the product are also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.

Also disclosed are pharmaceutical compositions containing the product and methods for its use in medicine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4562181 19851231 <--
AI US 1983-518693 19830729 (6) <--
PRAI GB 1982-22019 19820730 <--
AB There is described a product which is a highly pure substantially amorphous form of **cefuroxime axetil** (cefuroxime 1-acetoxyethyl ester) which is stable, which has increased absorption via the gastro-intestinal tract and has a correspondingly high level. .
.
AB . . . also described which involve the recovery of the product from a solution thereof. A preferred method is the use of **spray drying** techniques, though roller drying, solvent precipitation or freeze-drying are also described.
SUMM This invention relates to a novel, amorphous form of the 1-acetoxyethyl ester of cefuroxime(**cefuroxime axetil**), to a process for the preparation thereof, to a composition containing it and to its use in medicine.
SUMM Of the esters described in British Patent Specification No. 1571683, we have found **cefuroxime axetil** to be of particular interest. The processes for the preparation of the above ester exemplified in British Patent Specification No.. . .
SUMM In view of past experience in the cephalosporin field, we first prepared **cefuroxime axetil** for commercial evaluation in substantially pure, crystalline form. We have however surprisingly found that substantially pure, crystalline **cefuroxime axetil** does not have the best balance of properties for commercial use and that, contrary to previous experience in the cephalosporin field, **cefuroxime axetil** is advantageously used in a highly pure, substantially amorphous form. We have thus established that highly pure **cefuroxime axetil** when in substantially amorphous form has higher bioavailability upon oral administration than when in crystalline form and that moreover the amorphous form of **cefuroxime axetil** has adequate chemical stability upon storage. This is despite the known tendency for amorphous materials to have inferior chemical stability. . . known tendency for highly pure amorphous materials to crystallise. Thus, unlike previous cephalosporin compounds which have been developed for commercialisation, **cefuroxime axetil** is advantageously prepared and used in highly pure amorphous form rather than in crystalline form.
SUMM According to one aspect of the present invention, there is provided **cefuroxime axetil** in highly pure, substantially amorphous form.
SUMM The **cefuroxime axetil** in accordance with the invention preferably contains less than 5% mass/mass (m/m), advantageously less than 3% m/m, of impurities. It. . . `impurities` are to be understood as not including residual solvents remaining from the process used in the preparation of the **cefuroxime axetil** of the invention. Any residual solvent present will desirably only be present in less than 6% m/m and most preferably. . .
SUMM Typical impurities which may be present are the .DELTA..sup.2 -isomers of **cefuroxime axetil** and the corresponding E-isomers

of **cefuroxime axetil**.

SUMM The **cefuroxime axetil** ester in accordance with the invention is preferably essentially free from crystalline material.

SUMM **Cefuroxime axetil** possesses an asymmetric carbon atom at the 1-position of the 1-acetoxyethyl group and can therefore exist in the form of R and S isomers and mixtures thereof. The amorphous **cefuroxime axetil** ester according to the invention is preferably in the form of a mixture of its R and S isomers, such. . .

SUMM The **cefuroxime axetil** of the invention desirably has an E.sub.1 cm.sup.1 % at its .lambda..sub.max in methanol, when corrected for any solvent content, of from about 395 to 415. In addition, the **cefuroxime axetil** of the invention having an R to S isomer ratio of from 0.9:1 to 1.1:1, particularly of about 1:1 desirably. . . 1 and 2 of the accompanying drawings are respectively infra-red and n.m.r. spectra for specimens of highly pure, substantially amorphous **cefuroxime axetil** in accordance with the invention.

SUMM After absorption **cefuroxime axetil** is converted into the parent antibiotic acid cefuroxime which is known to exhibit high antibacterial activity against a broad range of gram-positive and gram-negative organisms. **Cefuroxime axetil** is thus useful in the oral or rectal treatment of a variety of diseases or infections caused by pathogenic bacteria.

SUMM The **cefuroxime axetil** according to the invention is conveniently prepared by a process which constitutes a further feature of the present invention and which comprises recovering **cefuroxime axetil** from a solution thereof under conditions whereby a highly pure, substantially amorphous product is obtained.

SUMM Techniques which may be employed to recover substantially amorphous **cefuroxime axetil** from the solution thereof include those wherein solvent is removed from the solution, preferably rapidly, and the product deposited and. . . wherein the product is precipitated from solution. Methods involving the use of these procedures which have been found satisfactory include **spray drying**, roller drying, solvent precipitation and freeze drying.

SUMM Solvents for **cefuroxime axetil** will be chosen according to the technique and conditions to be employed. Suitable solvents for dissolving **cefuroxime axetil** to form solutions from which recovery is enabled include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM The concentration of **cefuroxime axetil** in the solvent is with advantage as high as possible, commensurate with a substantially amorphous product being obtained, preferred concentrations being greater than 1% m/m, preferably greater than 10% m/m. The maximum concentration of the **cefuroxime axetil** in the solvent will depend upon the solvent used and in general will be less than 30% m/m. For example, the concentration of **cefuroxime axetil** in **acetone** will conveniently lie within the range 10 to 20% m/m. The solvents may if desired be heated as an aid. .

SUMM In general, we have found that the **cefuroxime axetil** has sufficient heat stability to withstand **spray drying** and accordingly **spray drying** is a preferred method of effecting recovery. **Spray drying** systems can be operated in known manner to obtain an amorphous product essentially free from crystalline material and free from particulate contaminants. Closed cycle **spray drying** systems in which the drying medium is recycled are particularly safe and economic for use in obtaining the product of. . .

SUMM When employing **spray drying**, suitable solvents for dissolving **cefuroxime axetil** prior to **spray drying** include organic solvents, for example ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the

form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; esters, e.g. methyl. . .

SUMM . . . inert gases such as nitrogen, argon and carbon dioxide being preferred in this case. The gas inlet temperature to the **spray dryer** will be chosen according to the solvent used, but may for example be in the range 50.degree.-140.degree. C. preferably 60.degree.-125.degree.. . .

SUMM The use of rapid evaporation techniques, in particular the use of **spray drying** also leads particularly readily to the formation, under appropriate conditions, of products having a consistent range of particle sizes. The product from **spray drying** has the form of hollow microspheres which can conveniently be compounded into pharmaceutical compositions.

SUMM When employing roller drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . .

SUMM When employing solvent precipitation, suitable solvents from which the **cefuroxime axetil** may be precipitated include ketones, e.g. **acetone**; alcohols, e.g. methanol or ethanol, if desired in the form of methylated spirits (e.g. IMS); acetonitrile; tetrahydrofuran; dioxan; esters, e.g.. . . this gives a homogeneous phase. Precipitation may be effected by the addition of appropriate quantities of a non-solvent for the **cefuroxime axetil** . Suitable non-solvents include water, alkanes and mixtures of alkanes, e.g. hexane or medium boiling range petrol (e.g. 60.degree.-80.degree. C.), ethers,. . . at least partially miscible and preferably fully miscible. Typical combinations of solvent and non-solvent are dichloromethane/isopropyl ether, ethyl acetate/petrol and **acetone**/water. The solid should be removed from solution as quickly as possible and dried as quickly as possible to avoid formation. . .

SUMM . . . technique of solvent precipitation may usefully be applied to the reaction mixture remaining after an esterification reaction in which the **cefuroxime axetil** has been formed in order to obtain amorphous **cefuroxime axetil** directly. This may be achieved by the addition of a solvent e.g. an ester such as ethyl acetate to the. . .

SUMM When employing freeze-drying, suitable solvents for dissolving the **cefuroxime axetil** prior to drying include dioxan and t-butanol. The temperature at which the recovery will be effected will depend upon the. . .

SUMM In order to obtain **cefuroxime axetil** ester in highly pure form by the above techniques it is necessary to employ a starting material of suitable purity--i.e.. . .

SUMM The solution from which the **cefuroxime axetil** is recovered preferably contains a mixture of both R- and S-isomers, whereby the product is obtained as a mixture of. . . general, the R/S isomer ratio of the product in solution is exactly reflected in the final product obtained e.g. by **spray drying**, and this ratio for the final product can accordingly be controlled if desired by adjustment of the R/S isomer ratio. . .

SUMM The **cefuroxime axetil** ester according to the invention may be formulated for oral (including buccal) or rectal administration.

SUMM . . . Such pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable **excipients** such as binding agents e.g. pregelatinised maize starch, polyvinyl-pyrrolidone or hydroxypropyl-**methylcellulose**; fillers e.g. starch, **lactose**, micro-crystalline **cellulose** or calcium phosphates; lubricants e.g. magnesium **stearate**, hydrogenated vegetable oils, talc, silica, polyethyleneglycols; disintegrants e.g. potato starch or sodium **starch glycolate**; or wetting agents e.g. sodium lauryl sulphate. Flow aids e.g. silicon dioxide may

also be used if desired. The tablets. . .

SUMM The preparation of a composition suitable for forming into tablets, capsules or granules may also be achieved by **spray-drying** or roller drying a suspension of pure amorphous **cefuroxime axetil** with the **excipients** appropriate for the said tablets, capsules or granules.

SUMM . . . liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents e.g. sorbitol syrup, methyl **cellulose** or hydrogenated edible fats and oils such as hydrogenated castor oil; emulsifying or thickening agents e.g. lecithin, aluminium **stearates** or acacia; non-aqueous vehicles e.g. almond oil, fractionated coconut oil, oily esters or ethyl alcohol; and preservatives e.g. methyl or. . .

SUMM The **cefuroxime axetil** of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository. . .

SUMM In a further aspect therefore the invention provides a pharmaceutical composition comprising **cefuroxime axetil** in highly pure, substantially amorphous form, in admixture with one or more pharmaceutical carriers and/or **excipients**. Such compositions are preferably adapted for absorption via the gastrointestinal tract, e.g. for oral administration. In a preferred embodiment, such. . .

SUMM . . . comprises administering to the said body orally or rectally an effective amount of a highly pure, substantially amorphous form of **cefuroxime axetil**.

DETD The following non-limiting Examples illustrate the invention. In all these Examples, the **cefuroxime axetil** starting materials used were in highly pure crystalline form. Such starting materials may for example be obtained by processes as described in British Pat. No. 1571683, or may alternatively be prepared by the crystallisation of highly pure **cefuroxime axetil** from an organic solvent, for example an ester such as ethyl acetate in admixture with an ether such as isopropyl. . .

DETD . . . by hydrolysis in situ at a temperature of +10.degree. to +30.degree. C. and crystallisation by addition of sodium 2-ethylhexanoate in **acetone** or methyl acetate as solvent.

DETD Crystalline **Cefuroxime Axetil**

DETD . . . washed with 2:1 diisopropyl ether/ethyl acetate (150 ml) and dried for a weekend in vacuo at 50.degree. to give crystalline **cefuroxime axetil** (19.3 g).

DETD A 10% m/v **acetone** solution of a mixture of R and S isomers of **cefuroxime axetil** was put through a Niro Mobile Minor **Spray Drier**, supplied by Niro Copenhagen, Denmark, using air as the drying gas and a rotary atomizer running at about 35,000 rpm. The gas inlet and outlet temperatures were 124.degree. and 70.degree. respectively. A recovery of 75% m/m of **spray dried** product was obtained. The microscopic appearance was typical for a **spray dried** product (hollow spheres). Assay by HPLC was 97% m/m and impurities by HPLC 2.0% m/m, both calculated to dry from. . .

DETD A mixture of R and S isomers of **cefuroxime axetil** (20.25 g) was dissolved in **acetone** (200 ml) at ambient temperature. The solution was clarified through sintered glass and pumped through a two fluid atomizer jet, using nitrogen under 1 kg/cm.sup.2 as the atomising fluid, into the glass drying chamber of a Mini Spray HO **spray drying** apparatus using an approximately 50:50 mixture of air and nitrogen as the drying gas. The gas inlet and outlet temperatures were 75.degree. and 55.degree. respectively. The recovery was 14.1 g (70.5%) of amorphous material containing 1.1% m/m **acetone** (GLC). Impurities (by HPLC) 1.7% m/m including 0.2% m/m ceph-2-em compound. Isomer ratio 1.03:1. .nu..sub.max (Nujol) similar to that shown. . .

DETD A 15% **acetone** solution of **cefuroxime axetil** (ca 1:1 mixture of R and S isomers) was put through a closed cycle **spray dryer** using nitrogen as the recycling gas and a rotating wheel atomiser running at 24,000 rpm. The gas inlet and outlet

temperatures were 105.degree. and 70.degree. respectively. The recycling gas was cooled to remove most of the evaporated **acetone**. Recovery of amorphous product was 90% with an **acetone** content of 1.0% m/m (GLC), water 0.7% m/m (Karl Fischer), HPLC impurity level 1.3% m/m. Infrared (Nujol) (KBr plates) and. . .

DETD Further Examples 4 to 17 illustrating the preparation of amorphous **cefuroxime axetil** are given in the following Table. The process of these examples was similar to that of Example 2. The Nujol. . .

DETD

Ex No.	Solvent	Inlet Temp .degree.C.	Outlet Temp .degree.C.
4.	**Acetone**/water	62	55
5.	Industrial methylated spirit	80	70
6.	Acetonitrile	72	63
7.	Tetrahydrofuran	75	65
8.	Methylacetate	63	55
9.	Chloroform (water set)	64	58
10.	**Acetone**/water	70	50
11.	Ethylacetate/water	72	64
12.	Methylacetate/water	64	57
13.	Methanol/water	67-70	55-59
14.	Methanol/**acetone**	63	54
15.	Ethanol/**acetone**	83	65
16.	**Acetone**/methylacetate	63	54
17.	**Acetone**	85-90	75

DETD A solution of purified crystalline cefuroxime 1-acetoxyethyl ester (isomer A) (77 g) in **acetone** (1.8 liters) at 45.degree. was **spray dried** as in Example 2 through a two fluid atomizer nozzle with a nitrogen atomizing pressure of 0.5 kg/cm.sup.2. The gas inlet temperature was 85.degree.-90.degree. and the outlet temperature ca 75.degree.. The product (39 g) had an **acetone** content of 0.15% m/m and impurities by HPLC of 2.8% m/m. The infrared spectrum (Nujol) confirmed the amorphous nature of. . .

DETD A mixture of the R and S isomers of **cefuroxime axetil** (10 g) was dissolved in hot **acetone** (70 ml) and evaporated in vacuo to a froth. This was broken up and dried overnight in vacuo at 40.degree. to give 9.8 g of **cefuroxime axetil** which was shown by IR (Nujol) (which was similar to that in FIG. 1) and microscopic examination to be amorphous. The **acetone** content (GLC) was 2.9%. Impurities by HPLC were 3.4% m/m and the isomer ratio was 1.14:1.

DETD Following the above procedure, pure amorphous **cefuroxime axetil** was also obtained using IMS, methanol and ethyl acetate as solvents.

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (5 g) was dissolved in boiling ethylacetate (200 ml) and concentrated at atmospheric pressure to 70 ml. The solution was. . . displacement washed with petroleum ether (bp. 60.degree.-80.degree.) and dried overnight in vacuo at 50.degree. to give 4.5 g of amorphous **cefuroxime axetil**. Solvent content (GLC) 0.25% m/m; [.alpha.].sub.D (1% in dioxan)+39.degree.; E.sub.1 cm.sup.1 % (MeOH) 388. Microscopic examination confirmed the amorphous nature. . .

DETD A ca 1:1 mixture of the R and S isomers of **Cefuroxime axetil** (6 g) was dissolved in boiling dichloromethane (240 ml), allowed to cool and filtered. The filtrate was distilled to a. . .

filtered, washed with di-isopropyl ether (100 ml) and dried overnight in vacuo at 50.degree. to give 5.5 g of amorphous **cefuroxime axetil**. Microscopic examination suggested <1% crystalline material. [.alpha.].sub.D (1% dioxan)+36.degree., E.sub.1 cm.sup.1 % 387 (MeOH). Solvent content (GLC), 1%,

DETD . . . nitrogen was bubbled in at 12 l min.sup.-1. A solution of a mixture of the R and S isomers of **cefuroxime axetil** (200 g) dissolved in a warm (45.degree.) mixture of **acetone** (600 ml) and water (66 ml) was then added with the aid of a peristaltic pump at a constant rate over 13 minutes into the vortex of the water. The precipitated amorphous **cefuroxime axetil** was carried through the horizontal aperture as a froth and collected. The amorphous **cefuroxime axetil** product was harvested immediately and dried to constant weight in vacuo at 55.degree. to yield 170 g. Solvent content (GLC)<0.01. . .

DETD A ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (100 g) was dissolved by stirring in **acetone** (1 l) and warming to 40.degree.. The rollers of a drier were heated to 75.degree., steam (two bar pressure) was. . . jacket and 737 mm vacuum applied to the apparatus. Using a roller speed of 1.75 rpm the prepared solution of **cefuroxime axetil** was sucked in at a rate of ca 200 ml/min. The product was knifed from the rollers and collected in. . .

DETD A solution of a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (10 g) in dioxan (100 ml) was freeze dried to give the product (10.7 g) which contained dioxan 5.5% m/m. .

DETD . . . of petrol (105 ml) and ethyl acetate (12 ml) followed by petrol (118 ml). Drying at 40.degree. in vacuo gave **cefuroxime axetil** 17.9 g: Solvents (GLC), ethylacetate 1.6%, petrol 1.5%; impurities by HPLC 4.1% m/m, isomer ratio 1.06:1; E.sub.1 cm.sup.1 % (MeOH). . .

DETD **Acetone** (2000 ml), water (324 ml) and IMS (36 ml) were added to a stirred flask followed by a ca 1:1 mixture of the R and S isomers of **cefuroxime axetil** (600 g). The contents of the flask were heated to 42.degree. and stirred until the solid dissolved. Immediately prior to. . .

DETD Water (850 ml/min) and the **cefuroxime axetil** solution (115 ml/min) was added simultaneously into the turbulent zone in the precipitator. The overflow from the precipitator was directed. .

DETD . . . dried in vacuo at 45.degree. until the moisture content was reduced to less than 1% to yield 410 g of **cefuroxime axetil**.

DETD

1. Tablet

Composition	mg/tablet
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Starch 1500 (Colorcon, Inc) (Pregelatinised starch)	161.5
Sodium **Starch Glycolate**	20.0
Sodium Lauryl Sulphate	10.0
Polyethylene glycol 6000 (micronized)	7.5
Silicon Dioxide	1.0
Total weight	500.0

DETD The polyethylene glycol, sodium lauryl sulphate, sodium **starch glycolate** and silicon dioxide were passed through a 60 mesh screen and blended with a small quantity of the active ingredient.. .

DETD The tablet may then be film coated with **cellulose** derivatives with plasticisers, colouring agents and preservatives if necessary, using aqueous or organic solvent methods.

DETD

2. Capsule

Composition	mg/capsule
Cefuroxime axetil according to the invention	300.00 (equivalent to 250 mg cefuroxime)
Microcrystalline **cellulose**	24.75
Hydrogenated Vegetable Oil	4.0
Sodium Lauryl Sulphate	9.0
Silicon Dioxide	1.25

DETD

3. Powder for oral suspension (in sachet)

Composition (per sachet)

Cefuroxime axetil according to the invention	300	mg
Sodium lauryl sulphate	25	mg
Hydroxypropyl-methyl-**cellulose**	90	mg
Spray dried orange flavour	150	mg
Castor sugar to	2220	mg

DETD The sodium lauryl sulphate, hydroxypropylmethyl-**cellulose** and flavour were triturated with the active ingredient. This blend was then further blended with castor sugar, adding the latter. . .

DETD

4. Oily Suspension

Composition (per 5 ml dose)

Cefuroxime axetil according to the invention	300	mg
Lecithin	35	mg
Butylhydroxybenzoate	2	mg
Aluminium monostearate	25	mg
Aluminium distearate	25	mg
Hydrogenated castor oil	17.5	mg

Liquid flavour. . .

DETD Some of the coconut oil was heated, then the lecithin, butylhydroxybenzoate aluminium **stearates**, hydrogenated castor oil, icing sugar and sodium chloride were added to the oil with mixing.

DETD The mixture was cooled and the **cefuroxime axetil** and flavour added. The remainder of the required coconut oil was then added and the preparation was mixed and refined.

CLM What is claimed is:

1. **Cefuroxime axetil** in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents.

. . .

. . . comprises administering to the said body orally or rectally an effective amount of a highly pure substantially amorphous form of **cefuroxime axetil** as claimed in claim 1.

8. An antibacterial pharmaceutical composition containing an antibacterially effective amount of **cefuroxime axetil**

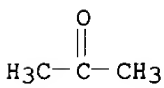
according to claim 1 in admixture with one or more pharmaceutical carriers or **excipients**.

9. The antibacterial pharmaceutical composition of claim 8 wherein the **cefuroxime axetil** is present in the form of a mixture of R and S isomers.

12. The antibacterial pharmaceutical composition of claim 8 wherein the **cefuroxime axetil** is in the form of hollow microspheres.

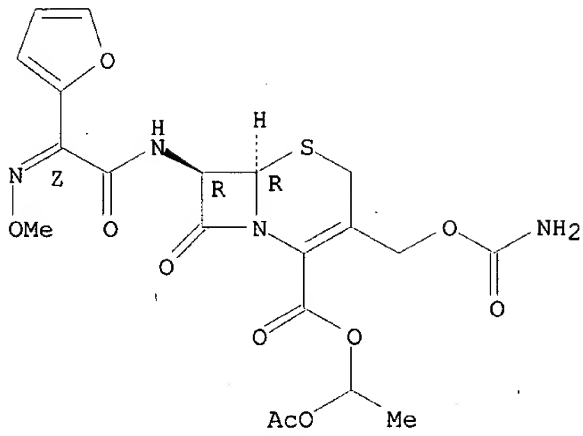
14. The antibacterial pharmaceutical composition of claim 13 in dosage unit form containing from 50 to 500 mg of **cefuroxime axetil**.

IT 64-17-5, uses and miscellaneous 67-56-1, uses and miscellaneous **67-64-1**, uses and miscellaneous 67-66-3, uses and miscellaneous 75-05-8, uses and miscellaneous 75-09-2, uses and miscellaneous 79-20-9 108-20-3 109-99-9, uses and miscellaneous 123-91-1, uses and miscellaneous 141-78-6, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)
IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)
IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)
IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)
IT **67-64-1**, uses and miscellaneous
(in prepn. of amorphous cefuroxime axetil, for pharmaceuticals)
RN 67-64-1 USPATFULL
CN 2-Propanone (9CI) (CA INDEX NAME)



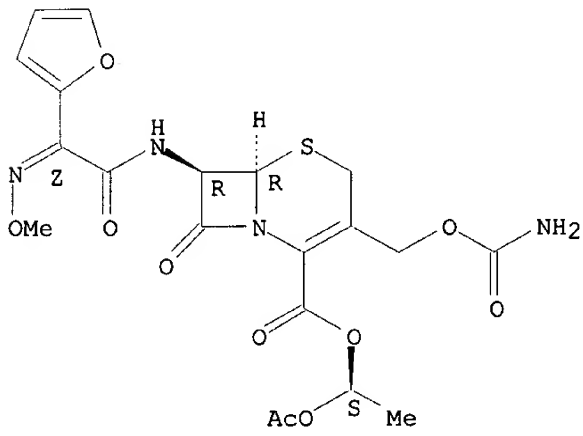
IT **64544-07-6P**
(prepn. of amorphous mixts. of, for pharmaceuticals enhanced bioavailability)
RN 64544-07-6 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



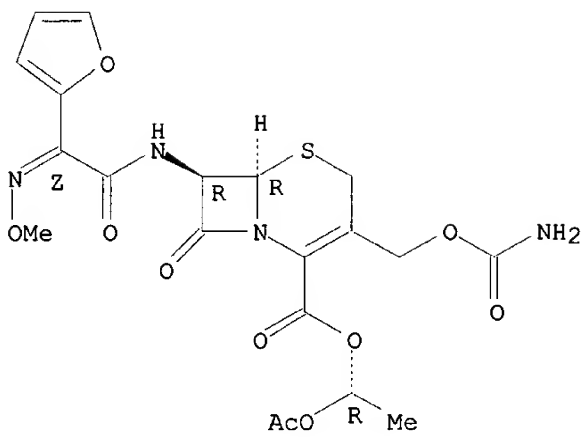
IT **64599-29-7P**
(prepn. of amorphous mixts. with R isomer, for pharmaceuticals with enhanced bioavailability)
RN 64599-29-7 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1S)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **64599-28-6P**
(prepn. of amorphous mixts. with S isomer, for pharmaceuticals with enhanced bioavailability)
RN 64599-28-6 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1R)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L66 ANSWER 5 OF 5 USPATFULL
AN 81:26252 USPATFULL
TI Cephalosporin antibiotics
IN Gregson, Michael, Middlesex, England
Sykes, Richard B., Chalfont St. Giles, England
PA Glaxo Laboratories Limited, England (non-U.S. corporation)
PI US 4267320 19810512 <--
AI US 1979-61260 19790727 (6) <--
RLI Continuation of Ser. No. US 1978-921120, filed on 30 Jun 1978, now abandoned which is a continuation of Ser. No. US 1977-768720, filed on 15 Feb 1977, now abandoned
PRAI GB 1976-6009 19760216 <--
GB 1976-27301 19760630 <--
GB 1976-27302 19760630 <--
DT Utility
EXNAM Primary Examiner: Coughlan, Jr., Paul M.
LREP Bacon & Thomas
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 619
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides novel antibiotic cefuroxime esters of the formula ##STR1## (wherein R.sup.1 is a primary or secondary alkyl group containing 1 to 4 carbon atoms and R.sup.2 is a primary or secondary alkyl group containing 1 to 6 carbon atoms provided that at least one of the groups R.sup.1 and R.sup.2 is methyl). These compounds are useful as orally administrable broad spectrum antibiotics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4267320 19810512 <--
AI US 1979-61260 19790727 (6) <--
PRAI GB 1976-6009 19760216 <--
PRAI GB 1976-27301 19760630 <--
PRAI GB 1976-27302 19760630 <--
SUMM . . . in solution in an inert organic solvent (e.g. an N,N-disubstituted amide such as N,N-dimethylformamide or N,N-dimethylacetamide, a ketone such as **acetone**, a sulphoxide such as dimethylsulphoxide, a nitrile such as acetonitrile, or hexamethylphosphoric triamide) at a temperature in the range -50.degree.. . .
SUMM . . . may be formulated as compositions for oral administration in conventional manner, with the aid of any necessary pharmaceutical carriers or **excipients**. The compositions are conveniently prepared as tablets, capsules or sachets, advantageously in unit dose form, and may contain conventional **excipients** such as binding

agents, fillers, lubricants, disintegrants and wetting agents. Tablets may be coated in conventional manner. The active compounds. . .

DETD

Composition:

1-Acetoxyethyl (6R,7R)-3-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido] ceph-3-em-4-carboxylate (micronised)	326.0 mg
Sodium **starch glycolate** (Primojel)	8.0 mg
Microcrystalline **cellulose** (Avicel PH101)	64.0 mg
Magnesium **stearate**	2.0 mg
Total weight	400.0 mg

DETD The magnesium **stearate** was blended with the active ingredient and tablet slugs/were prepared by direct compression. The slugs were broken down through 12 mesh, 16 mesh and 20 mesh consecutively and the granules were blended with the sodium **starch glycolate** and microcrystalline **cellulose**. The blend was compressed on concave punches to a tablet weight of 400 mg. The tablets may be film coated by the aqueous or organic solvent method using **cellulose** derivatives with plasticisers and colouring matter. As an alternative to the preliminary slugging stage, the active ingredient may be densified. . .

DETD

Composition (per sachet)

1-Acetoxyethyl (6R,7R)-3-carbamoyloxymethyl-7-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido] ceph-3-em-4-carboxylate (milled)	326.0 mg
Lecithin	25mg
Sodium carboxymethyl **cellulose** (low viscosity)	90mg
Spray-dried orange flavour	150mg
Caster sugar	2.2g

DETD . . . The chloroform was allowed to evaporate and the resultant solid powdered. It was then blended intimately with the sodium carboxymethyl **cellulose** and the flavour. This blend was then further blended with the caster sugar adding the latter in two stages. It. . .

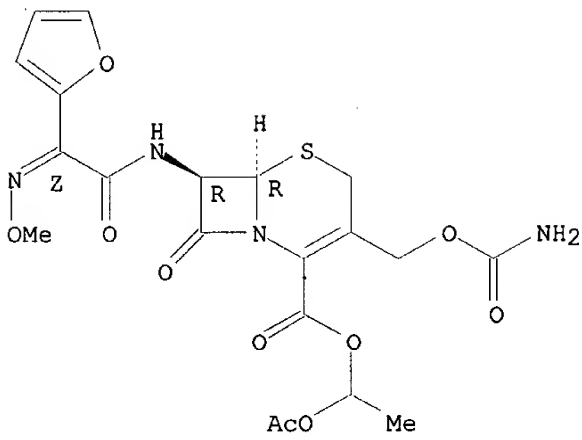
IT **64544-07-6P** 64544-08-7P 64544-09-8P 64544-10-1P 64544-11-2P 64544-12-3P 64544-13-4P 64544-14-5P **64599-28-6P** **64599-29-7P**
(prepn. of)

IT **64544-07-6P** **64599-28-6P** **64599-29-7P**
(prepn. of)

RN 64544-07-6 USPATFULL

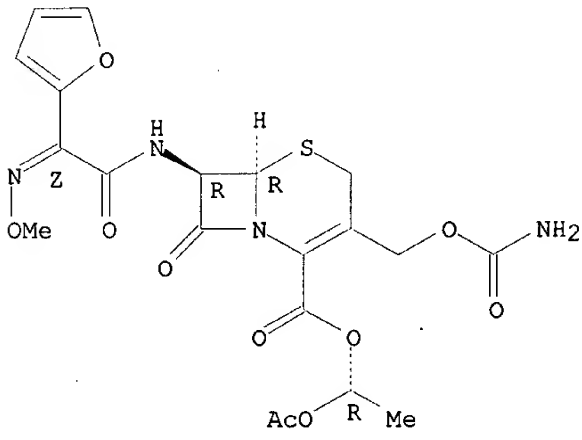
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



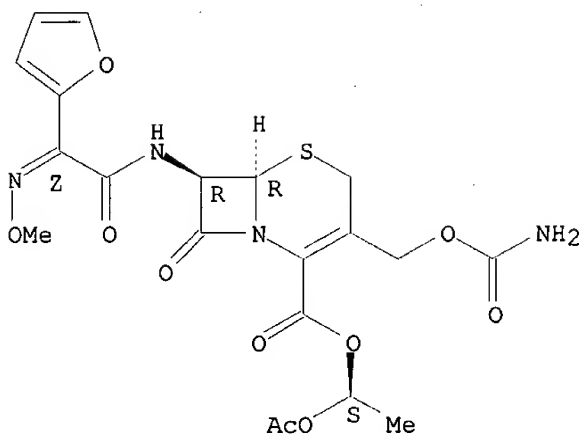
RN 64599-28-6 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1R)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 64599-29-7 USPATFULL
CN 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(aminocarbonyl)oxy]methyl]-7-[[(2Z)-2-furanyl(methoxyimino)acetyl]amino]-8-oxo-, (1S)-1-(acetyloxy)ethyl ester, (6R,7R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



=> d l67 bib abs kwic hitrn tot

L67 ANSWER 1 OF 13 USPATFULL
AN 2001:1789 USPATFULL
TI Oxazolone derivatives and their use as anti-Helicobacter pylori agent
IN Kanamaru, Tsuneo, Osaka, Japan
Nakao, Masafumi, Nara, Japan
Tawada, Hiroyuki, Osaka, Japan
Kamiyama, Keiji, Osaka, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6169102 20010102
WO 9749703 19971231
AI US 1998-142506 19980910 (9)
WO 1997-JP2157 19970624 <-- ,
19980910 PCT 371 date
19980910 PCT 102(e) date
PRAI JP 1996-164854 19960625 <--
JP 1997-25162 19970207 <--
DT Utility
EXNAM Primary Examiner: Stockton, Laura L.
LREP Fitzpatrick, Cella, Harper & Scinto
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3080
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An anti-Helicobacter pylori agent comprising a compound represented by the formula: ##STR1##

wherein A represents an aromatic ring group which may be substituted; R.sup.1 and R.sup.2, whether identical or not, each represent a hydrogen atom or a hydrocarbon group which may be substituted; R.sup.3 and R.sup.4, whether identical or not, each represent a hydrogen atom, a hydrocarbon group which may be substituted, an acyl group, a carbamoyl group which may be substituted, or a carboxyl group which may be esterified; or a salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1998-142506 19980910 (9)
WO 1997-JP2157 19970624 <--
19980910 PCT 371 date
19980910 PCT 102(e) date
PRAI JP 1996-164854 19960625 <--
PRAI JP 1997-25162 19970207 <--

SUMM . . . may be substituted, or a carboxyl group which may be esterified, or a salt thereof, and a pharmacologically acceptable diluent, **excipient** or carrier,

SUMM . . . may be substituted, or a carboxyl group which may be esterified, or a salt thereof with a pharmacologically acceptable diluent, **excipient** or/and carrier,

SUMM . . . above-mentioned dosage forms, known production methods in common use in relevant fields are applicable. In producing the above-mentioned dosage forms, **excipients**, binders, disintegrants, lubricants, sweetening agents, surfactants, suspending agents, emulsifiers etc. in common use in the field of pharmaceutical making may. . .

SUMM When compound (I) or a salt thereof is prepared as tablets, for example, **excipients**, binders, disintegrants, lubricants etc. may be contained; when compound (I) or a salt thereof is prepared as pills or granules, **excipients**, binders, disintegrants etc. may be contained. When compound (I) or a salt thereof is prepared as powders or capsules, **excipients** etc. may be contained; when compound (I) or a salt thereof is prepared as syrups, sweetening agents etc. may be. . . or a salt thereof is prepared as emulsions or suspensions, suspending agents, surfactants, emulsifiers etc. may be contained. Examples of **excipients** include **lactose**, saccharose, glucose, starch, sucrose, microcrystalline **cellulose**, powdered glycyrrhiza, **mannitol**, sodium hydrogen carbonate, calcium phosphate and calcium sulfate. Examples of binders include 5-10% by weight starch glue solutions, 10-20% by weight gum arabic solutions or gelatin solutions, 1-5% by weight tragacanth solutions, carboxymethyl **cellulose** solutions, sodium alginate solutions and glycerol. Examples of disintegrants include starch and calcium carbonate. Examples of lubricants include magnesium **stearate**, **stearic acid**, calcium **stearate** and purified talc. Examples of sweetening agents include glucose, fructose, invert sugar, sorbitol, xylitol, glycerol and simple syrups. Examples of surfactants include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester and **stearic acid** polyoxyl 40. Example of suspending agents include gum arabic, sodium alginate, carboxymethyl **cellulose** sodium, methyl **cellulose** and bentonite. Examples of emulsifiers include gum arabic, tragacanth, gelatin and polysorbate 80.

SUMM . . . and metronidazole), tetracyclines (e.g., tetracycline, doxycycline and minocycline), penicillins (e.g., amoxicillin, ampicillin and mezlocillin), cephalosporins (e.g., cefaclor, cefadroxil, cefazolin, cefuroxime, **cefuroxime axetil**, cephalexin, cefpodoxime proxetil, ceftazidime and ceftriaxone), carbapenems (e.g., imipenem and meropenem), aminoglycosides (e.g., paromomycin), macrolide antibiotics (e.g., erythromycin, clarithromycin and. . .

SUMM . . . trichlene and 1,2-dichloroethane; hydrocarbons such as n-hexane, benzene and toluene; amides such as formamide, N,N-dimethylformamide and N,N-dimethylacetamide; ketones such as **acetone**, methyl ethyl ketone and methyl isobutyl ketone; nitriles such as acetonitrile and propionitrile; dimethyl sulfoxide, sulfolane, hexamethylphosphoramide and water; these. . .

SUMM . . . trichlene and 1,2-dichloroethane; hydrocarbons such as n-hexane, benzene and toluene; amides such as formamide, N,N-dimethylformamide and N,N-dimethylacetamide; ketones such as **acetone**, methyl ethyl ketone and methyl isobutyl ketone; nitriles such as acetonitrile and propionitrile; dimethyl sulfoxide, sulfolane, hexamethylphosphoramide and water; these. . .

SUMM . . . trichlene and 1,2-dichloroethane; hydrocarbons such as n-hexane, benzene and toluene; amides such as formamide, N,N-dimethylformamide and N,N-dimethylacetamide; ketones such as **acetone**, methyl ethyl ketone and methyl isobutyl ketone; nitriles such as acetonitrile and propionitrile; dimethyl sulfoxide, sulfolane, hexamethylphosphoramide are used as. . .

SUMM . . . trichlene and 1,2-dichloroethane; hydrocarbons such as n-hexane, benzene and toluene; amides such as formamide, N,N-dimethylformamide and N,N-dimethylacetamide; ketones such as

acetone, methyl ethyl ketone and methyl isobutyl ketone; nitriles such as acetonitrile and propionitrile; dimethyl sulfoxide, sulfolane, hexamethylphosphoramide and water; these. . .

SUMM . . . trichlene and 1,2-dichloroethane; hydrocarbons such as n-hexane, benzene and toluene; amides such as formamide, N,N-dimethylformamide and N,N-dimethylacetamide; ketones such as **acetone**, methyl ethyl ketone and methyl isobutyl ketone; nitriles such as acetonitrile and propionitrile; dimethyl sulfoxide, sulfolane, hexamethylphosphoramide and water; these. . .

SUMM . . . trichlene and 1,2-dichloroethane; hydrocarbons such as n-hexane, benzene and toluene; amides such as formamide, N,N-dimethylformamide and N,N-dimethylacetamide; ketones such as **acetone**,. methyl ethyl ketone and methyl isobutyl ketone; nitriles such as acetonitrile and propionitrile; dimethyl sulfoxide, sulfolane, hexamethylphosphoramide and water;

SUMM . . . containing pridham and gottlieb)

L-arabinose	-
D-xylose	-
D-glucose	++
D-fructose	+
Sucrose	-
Inositol	-
L-rhamnose	++
Raffinose	-
D-**mannitol**	-
Control	-

(Note)
++: relatively good growth
+: growth noted
.+-.: + or - indeterminable
-: no growth

SUMM Carbon sources include, for example, glucose, **lactose**, sucrose, maltose, dextrin, starch, glycerol, **mannitol**, sorbitol, oils and fats (e.g., soybean oil, olive oil, rice bran oil, sesame oil, lard oil, chicken oil); nitrogen sources. . .

SUMM . . . industrial purposes, it is advantageous to purify indolmycin from the extract obtained by adding an organic solvent such as methanol, **acetone**, butanol or ethyl acetate directly to the culture, with the cell separation operation omitted.

SUMM . . . is concentrated; the resulting concentrate is subjected to silica gel column chromatography. Useful developing solvents include, for example, chloroform-methanol or hexane-**acetone** mixed solvents. After the effective fractions are combined and concentrated, the concentrate is subjected to Sephadex LH-20 chromatography. Useful developing. . .

DETD . . . through a silica gel column (0.8 l) to adsorb the active ingredient, followed by sequential elution with 4 l of hexane-**acetone** (80:20), 4 l of hexane-**acetone** (50:50) and 4 l of hexane-**acetone** (20:80). The effective fractions were combined and concentrated under reduced pressure to yield 1.53 g of a concentrate. This concentrate. . .

DETD . . . was dried over MgSO.sub.4. Removal of the organic solvent gave a residue, which was subjected to silica-gel chromatography. Elution with hexane-**acetone** (4:1) provided the titled compound (176 mg, 70.4%). m.p. 146-148.degree. C.

DETD . . . was dried over MgSO.sub.4. Removal of the organic solvent gave a residue, which was subjected to silica-gel chromatography. Elution with hexane-**acetone** (5:1) provided the titled compound (534 mg, 73.3%).

DETD . . . was dried over MgSO.sub.4. Removal of the organic solvent gave a residue, which was subjected to silica-gel chromatography. Elution with hexane-**acetone** (3:1) provided the titled compound (154 mg, 71.6%).

DETD . . . was dried over MgSO.sub.4. Removal of the organic solvent gave a residue, which was subjected to silica-gel chromatography. Elution with hexane-**acetone** (4:1) provided the titled compound (387

mg, 83.3%).

DETD . . . at the same temperature. The mixture was concentrated to give a residue, which was subjected to column chromatography. Elution with hexane-**acetone** (1:1) provided the titled compound (254 mg).

DETD . . . over magnesium sulfate. The solution was concentrated to give a residue, which was subjected to silica gel chromatography. Elution with hexane-**acetone** (1:1) gave the titled compound (375 mg).

DETD . . . remove the catalyst. The filtrate was concentrated to give a residue, which was subjected to silica gel chromatography. Elution with hexane-**acetone** (1:1) provided the titled compound (72 mg).

DETD . . . magnesium sulfate. Concentration of the ethyl acetate solution gave a residue, which was subjected to silica gel chromatography. Elution with hexane-**acetone** (1:1) provided 2-dimethylamino-5-[1-(4-methoxyindol-3-yl)ethyl-2-oxazolin-4-one (54 mg).

DETD . . . for 2.5 hours. The-methylamine was distilled off to give a residue, which was subjected to silica gel chromatography. Elution with hexane-**acetone** (1:1) provided the titled compound (32 mg).

DETD . . . dried over magnesium sulfate. Concentration of the solution gave a residue, which was subjected to silica gel chromatography. Elution with hexane-**acetone** (1:1) provided the titled compound (25 mg).

DETD . . . over magnesium sulfate. Concentration of the solution gave a residue, which was subjected to silica gel chromatography. The eluent with hexane-**acetone** (1:1) was collected and concentrated to provide the titled compound (40 mg).

DETD . . . magnesium sulfate. Concentration of the solution gave a residue, which was subjected to the silica gel chromatography. The eluent with hexane-**acetone** (1:1) was collected and concentrated to provide the titled compound (16 mg).

DETD . . . infection, a 3, 10, 30, or 100 mg/kg suspension of the test compound in a 0.5% aqueous solution of methyl **cellulose** was orally administered twice daily (morning and evening) for 3 days. On the day after final administration, the stomach of. . .

DETD . . . 4

Test Compound	Dose (mg/kg)	Clearance Rate (%)	Bacterial Detection (log CFU/ gastric wall)
Control (0.5% methyl **cellulose** solution)	-- 0/4	(0)	6.36 .+-. 0.19
Indolmycin	3 0/5	(0)	4.61 .+-. 1.84
	10 0/5	(0)	2.76 .+-. 1.04**
	30 1/4	(25)	1.96 .+-. 0.78**
	100.	. .	

DETD 1. Capsules

(1)	Indolmycin	100	mg
(2)	**Lactose**	90	mg
(3)	Microcrystalline **cellulose**	70	mg
(4)	Magnesium **stearate**	10	mg
	Total	270	mg

per capsule

DETD 2. Tablets

(1)	Indolmycin	100	mg
(2)	**Lactose**	35	mg
(3)	Corn starch	150	mg
(4)	Microcrystalline **cellulose**	30	mg
(5)	Magnesium **stearate**	5	mg
	Total	320	mg

per tablet

CLM What is claimed is:

. . . alkoxy which is unsubstituted or substituted by 1 to 5 halogens), or a salt thereof; and a pharmacologically acceptable diluent, **excipient** or carrier.

L67 ANSWER 2 OF 13 USPATFULL
AN 2000:160591 USPATFULL
TI Compositions for targeting biological agents
IN Kabanov, Alexander V., Omaha, NE, United States
Alakhov, Valery Yu., Quebec, Canada
Chekhonin, Vladimir P., Moscow, Russian Federation
Batrakova, Elena V., Moscow, Russian Federation
Kabanov, Victor A., Moscow, Russian Federation
PA Supratek Pharma Inc., Canada (non-U.S. corporation)
PI US 6153193 20001128
AI US 1995-478979 19950607 (8) <--
RLI Continuation-in-part of Ser. No. US 1993-54403, filed on 28 Apr 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Wortman, Donna C.
LREP Mathews, Collins, Shepherd & Gould, P.A.
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1593
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Improved pharmaceutical compositions useful in targeting biological agents to particular tissue and compositions useful for administering biological agents to the brain.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1995-478979 19950607 (8) <--
DETD . . . subcutaneously, intraperitoneally, intra-arterially or intravenously. The compositions can be administered alone, or can be combined with a pharmaceutically-acceptable carrier or **excipient** according to standard pharmaceutical practice. For the oral mode of administration, the compositions can be used in the form of. . . syrups, elixirs, aqueous solutions and suspensions, and the like. In the case of tablets, carriers that can be used include **lactose**, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium **stearate**, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are **lactose** and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the compositions can be combined with. . . the art such as applicators or eye droppers. Such compositions can include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl **methylcellulose** or poly(vinyl alcohol), preservatives such as sorbic acid, EDTA or benzylchronium chloride, and the usual quantities of diluents and/or carriers.. . .
DETD . . . first generation cephalosporins such as cephapirin, cefaxolin, cephalexin, cephradine and cefadroxil; second generation cephalosporins such as cefamandole, cefoxitin, cefaclor, cefuroxime, **cefuroxime axetil**, cefonicid, cefotetan and ceforanide; third generation cephalosporins such as cefotaxime, ceftizoxime, ceftriaxone, cefoperazone and ceftazidime), tetracyclines (such as demeclocytetracycline, doxycycline,. . .
DETD . . . Chemicals, Germany) in octane. A reaction is initiated by adding a two-fold molar excess (with respect to the polypeptide) of **stearic acid** chloride in 0.2 ml of 0.1 M AOT.RTM. in octane to the mixture. The **stearic acid** chloride was obtained from staric acid (available from Reakhim, Russia) as described in Kabanov et al., Molek Biologiya (Russian), 22:. . . (Engl. edn.: 382-391), 1988. The reaction was conducted overnight at 25.degree. C. The product is precipitated three times with cold **acetone**, dissolved in RPMI 1640 medium and sterilely filtered through a 0.22 .mu.m filter. (The polyclonal antibody used in this experiment. . .
DETD The antibodies (Ab) to GFAP and .alpha.2-glycoprotein were modified with **stearic acid** residues as described in example 1. They were also covalently linked to PLURONIC.RTM. P85 as described by Kabanov et al.. . .

DETD . . . doxorubicin, (b) doxorubicin in 1% PLURONIC.RTM. P85, (c) doxorubicin in 10% PLURONIC.RTM. P85 containing 0.1 mg/ml of Ab modified with **stearic acid** chloride and (d) doxorubicin in 10% PLURONIC.RTM. P85 containing 0.1 mg/ml of Ab linked to PLURONIC.RTM. P85 were administered i.p.. . .

L67 ANSWER 3 OF 13 USPATFULL
AN 2000:137858 USPATFULL
TI Oral pharmaceutical composition with delayed release of active ingredient for reversible proton pump inhibitors
IN Sachs, George, Encino, CA, United States
Dietrich, Rango, Constance, Germany, Federal Republic of
PA BYK Gulden Lomberg Chemische Fabrik GmbH, Constance, Germany, Federal Republic of (non-U.S. corporation)
PI US 6132768 20001017
AI US 1995-498391 19950705 (8) <--
DT Utility
EXNAM Primary Examiner: Spear, James M.
LREP Jacobson, Price, Holman & Stern, PLLC
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 511
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An oral pharmaceutical composition of a reversible proton pump inhibitor in pellet or tablet form, wherein the reversible proton pump inhibitor is at least partly in slow-release form, is distinguished, on combined administration with an antimicrobially-active ingredient, by an enhanced action of rapid onset against disorders caused by Helicobacter.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1995-498391 19950705 (8) <--
SUMM . . . butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, **stearic acid**, toluenesulfonic acid, methanesulfonic acid and 3-hydroxy-2-naphthoic acid, the acids being used in the preparation of the salt in a ratio. . .
SUMM . . . as tetracyline, chlorotetracycline, oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, **cefuroxime axetil**, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin; or other different antibiotics,. . .
SUMM . . . ingredients which may be emphasized are erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, ampicillin, mezlocillin, amoxicillin, tetracycline, minocycline, doxycycline, imipenem, meropenem, cefalexin, **cefuroxime axetil**, cefpodoxime proxetil, cefaclor, cefadroxil, ciprofloxacin, norfloxacin, of loxacin and pefloxacin.
SUMM . . . ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet ancillary substances and other active ingredient **excipients** it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between the active ingredients. . .
SUMM . . . polymerization. Examples of lubricants and nonstick agents are higher fatty acids and their alkali-metal and alkaline-earth-metal salts, such as calcium **stearate**. Suitable tablet disintegrants are, in particular, chemically-inert agents. Preferred tablet disintegrants include cross-linked polyvinylpyrrolidone, crosslinked sodium **carboxymethylcelluloses** and sodium **starch glycolate**.
SUMM . . . film polymers, in respect of the water-insoluble release-slowing intermediate layer(s) to be applied to the pellet or tablet core, include **ethylcellulose**, polyvinyl acetate,

Eudragit.RTM. RS, Eudragit.RTM. RL, etc. The release rate can be controlled not only by incorporating suitable water-soluble pore formers, such as PEG, **lactose**, **mannitol**, sorbitol, HPMC, etc., but also by the thickness of the coating layer applied.

SUMM It is possible in a similar way to use osmotic systems with semipermeable membranes of **cellulose** acetate, **cellulose** acetate butyrate or **cellulose** acetate propionate (as described in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,036,227, U.S. Pat. No.. . .

SUMM . . . of suitable polymers for the enteric coating are methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit.RTM. L) or **cellulose** derivatives, such as **carboxymethylethylcellulose** (CMEC, Duodcel), **cellulose** acetate phthalate (CAP), **cellulose** acetate trimellitate (CAT), **hydroxypropylmethylcellulose** phthalate (HP50, HP55), **hydroxypropylmethylcellulose** acetate succinate (HPMCAS) or polyvinyl acetate phthalate, to which it is also possible to add, if desired, plasticizer (such as. . .

DETD

a)	B9401-011 (hemimalate)	119.8 mg
b)	Sodium carboxymethylstarch	21.0 mg
c)	Microcrystalline **cellulose**	21.0 mg
	(e.g.: Avicel PH 101	
d)	Maize starch	19.4 mg
e)	Magnesium **stearate**	5.0 mg
		186.2 mg

DETD

f)	**Ethylcellulose**	9.85 mg
g)	**Lactose** micronized	2.37 mg
h)	Propylene glycol	0.98 mg
		14.00 mg

DETD

f)	Polyvinyl acetate	10.38 mg
g)	**Lactose** micronized	2.59 mg
h)	Propylene glycol	1.03 mg
		13.13 mg

DETD f) is dissolved in 150 ml of a 1:1 **acetone**/chloroform mixture. h) is stirred in for a sufficient length of time, using a suitable agitator to prepare a solution (A).

DETD g) is suspended in 150 ml of a 1:1 **acetone**/chloroform mixture, using rotor-stator agitator to prepare a fine dispersion (B). (A) and (B) are combined.

DETD

a)	Sucrose pellets (0.7-0.85 mm)	950.0 g
b)	**Hydroxypropylmethylcellulose**	40.0 g
	2910 (USP)	
c)	Propylene glycol	10.0 g

DETD

d)	B9401-011 (Hemimalate)	403.0 g

e) **Hydroxypropylmethylcellulose**
403.0 g
2910 (USP)
f) Propylene glycol 201.5 g

DETD

a) B9401-011 (Hemimalate)
403.0 g
b) Microcrystalline **cellulose**
117.0 g
(Avicel PH101)
c) Na **carboxymethylcellulose**
18.0 g

DETD a) and b) are premixed dry and subsequently moistened to a paste-like consistency with a solution of Na **carboxymethylcellulose** in water in a conventional kneader or high-speed mixer. The resulting composition is then extruded and shaped into pellets by. . .

CLM What is claimed:

. . . penicillin G, penicillin V, ampicillin, mezlocillin, amoxicillin, bacitracin, polymyxin, tetracycline, chlorotetracycline, oxytetracycline, minocycline, doxycycline, imipenem, loracarbef, meropenem, panipenem, cefalexin, cefoxitin, **cefuroxime axetil**, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil, cephalothin, ciprofloxacin, norfloxacin, ofloxacin, pefloxacin and chloramphenicol.

IT 56-75-7, Chloramphenicol 57-62-5 57-92-1, Streptomycin, biological studies 59-87-0, Nitrofurazone 60-54-8, Tetracycline 61-33-6, Penicillin G, biological studies 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 69-53-4, Ampicillin 79-57-2, Oxytetracycline 87-08-1, Penicillin V 114-07-8, Erythromycin 153-61-7, Cephalothin 443-48-1, Metronidazole 564-25-0, Doxycycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 1405-87-4, Bacitracin 1406-11-7, Polymyxin 6506-37-2, Nimorazole 8063-07-8, Kanamycin 10118-90-8, Minocycline 13292-46-1, Rifampicin 14882-18-9, Bismuth subsalicylate 15686-71-2, Cefalexin 18323-44-9, Clindamycin 19387-91-8, Tinidazole 26787-78-0, Amoxicillin 35607-66-0, Cefoxitin 37517-28-5, Amikacin 50370-12-2, Cefadroxil 51481-65-3, Mezlocillin 53994-73-3, Cefaclor 57644-54-9, Bismuth subcitrate 63527-52-6, Cefotaxime 64221-86-9, Imipenem **64544-07-6**, Cefuroxime axetil 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 76081-98-6 76470-66-1, Loracarbef 79707-34-9 81103-11-9, Clarithromycin 82419-36-1, Ofloxacin 83905-01-5, Azithromycin 85721-33-1, Ciprofloxacin 87239-81-4, Cefpodoxime proxetil 87726-17-8, Panipenem 96036-03-2, Meropenem 96428-79-4 115607-61-9 125500-29-0 158364-57-9 158364-58-0 158364-59-1 158364-63-7 158364-64-8 158364-65-9 158364-66-0 158364-67-1 158364-68-2 158364-69-3 158364-70-6 169319-20-4 169319-21-5 169319-22-6 169319-24-8
(oral compns. with delayed release of reversible proton pump inhibitors and antimicrobial agents)

IT **64544-07-6**, Cefuroxime axetil
(oral compns. with delayed release of reversible proton pump inhibitors and antimicrobial agents)

L67 ANSWER 4 OF 13 USPATFULL
AN 1999:102514 USPATFULL
TI Oral pharmaceutical composition with delayed release of active ingredient for pantoprazole
IN Sachs, George, Encino, CA, United States
Dietrich, Rango, Constance, Germany, Federal Republic of
PA BYK Gulden Chemische Fabrik GmbH, Constance, Germany, Federal Republic of (non-U.S. corporation)
PI US 5945124 19990831
AI US 1995-498386 19950705 (8) <--

DT Utility
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Spear, James M.
LREP Jacobson, Price, Holman & Stern, PLLC
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 513
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An oral pharmaceutical composition of pantoprazole in pellet or tablet form, wherein the pantoprazole is at least partly in slow-release form, is distinguished, on combined administration with an antimicrobially-active ingredient, by an enhanced action of rapid onset against disorders caused by Helicobacter.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1995-498386 19950705 (8) <--
SUMM . . . coated with a water-soluble intermediate layer and with an enteric layer, where improved stability is achieved by using polyvinylpyrrolidone and/or **hydroxypropylmethylcellulose** as binder for the alkaline core.
SUMM . . . and the enteric coating and is composed of a film-forming material which has only low solubility in water, such as **ethylcellulose** and polyvinyl acetate, and of a fine-particle inorganic or organic material which is suspended therein and has low solubility in. . .
SUMM . . . composition for acid-labile active ingredients which comprises (under the enteric coating) an intermediate layer of a film-forming material, such as **hydroxypropylmethylcellulose**, **hydroxypropylcellulose** and **hydroxypropylmethylcellulose** phthalate with a content of higher fatty acids.
SUMM DE-A 3233764 proposes for enteric compositions an intermediate layer which is formed from a water-soluble **cellulose** ether and a water-soluble mono- or polybasic organic acid, such as citric acid, tartaric acid, and the like.
SUMM . . . as tetracyline, chlorotetracycline, oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, **cefuroxime axetil**, cefotaxime, cefpodoxim proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin, or other different antibiotics,. . .
SUMM . . . ingredients which may be emphasized are erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, ampicillin, mezlocillin, amoxicillin, tetracycline, minocycline, doxycycline, imipenem, meropenem, cefalexin, **cefuroxime axetil**, cefpodoxime proxetil, cefaclor, cefadroxil, ciprofloxacin, norfloxacin, ofloxacin and pefloxacin.
SUMM . . . ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet auxiliary substances and other active ingredient **excipients** it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between the active ingredients. . .
SUMM . . . ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvents, tablet ancillary substances and other active ingredient **excipients** it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, dyes, etc. Where incompatibilities between the active ingredients. . .
SUMM . . . and nonstick agents which may be mentioned are higher fatty acids and their alkali-metal and alkaline-earth-metal salts, such as calcium **stearate**. Suitable tablet disintegrants are, in particular, chemically inert agents. Tablet disintegrants which may be mentioned as preferred are crosslinked polyvinylpyrrolidone, crosslinked sodium **carboxymethylcelluloses** and sodium **starch glycolate**.

SUMM . . . which can be used in the water-insoluble release-slowing intermediate layer(s) (to be applied to the pellet or tablet core) include **ethylcellulose**, polyvinyl acetate, Eudragit.RTM. RS, Eudragit.RTM. RL, etc. (Each of Eudragit.RTM. RS and Eudragit.RTM. RL is an ammonio methacrylate copolymer.) The release rate can be controlled not only by incorporating therein suitable water-soluble pore formers, such as PEG, **lactose**, **mannitol**, sorbitol, HPMC, etc., but also by the thickness of the coating layer applied.

SUMM It is possible in a similar way to use osmotic systems with semipermeable membranes of **cellulose** acetate, **cellulose** acetate butyrate, **cellulose** acetate propionate, as described in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,036,227, U.S. Pat. No.. . .

SUMM . . . of suitable polymers for the enteric coating are methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit.RTM. L) or **cellulose** derivatives, such as **carboxymethylethylcellulose** (CMEC, Duodcel), **cellulose** acetate phthalate (CAP), **cellulose** acetate trimellitate (CAT), **hydroxypropylmethylcellulose** phthalate (HP50, HPSS), **hydroxypropylmethylcellulose** acetate succinate (HPMCAS) or polyvinyl acetate phthalate, to which it is also possible to add, if desired, plasticizer (such as. . .

DETD

a)	Pantoprazole Na .times. 1.5 H2O	45.1	mg
b)	Sodium carbonate	10.0	mg
c)	**Mannitol**	20.0	mg
d)	EPMC 2910 3 cps	25.0	mg
e)	HPMC 2910 15 cps	4.0	mg
f)	Calcium **stearate**	2.1	mg
		106.2	mg

DETD

g)	**Ethylcellulose**	9.85	mg
h)	**Lactose** micronized	2.37	mg
i)	Propylene glycol	0.98	mg
j)	Ammonia 25%	0.80	mg
		14.00	mg

DETD

g)	Polyvinyl acetate	9.15	mg
h)	**Lactose** micronized	2.27	mg
i)	Propylene glycol	0.91	mg
j)	Ammonia 25%	0.80	mg
		13.13	mg

DETD g) is dissolved in 150 ml of a 1:1 **acetone**/chloroform mixture to prepare a solution (A).

DETD A fine dispersion of h) in 150 ml of a 1:1 **acetone**/choroform mixture is prepared using a rotor-stator agitator, and subsequently i) and j) are stirred in using a suitable agitator to. . .

DETD

I. Starter Pellets

a)	Sucrose pellets (0.7-0.85 mm)	950.0	g
b)	**Hydroxypropylmethylcellulose** 2910 (USP)	40.0	g
c)	Propylene glycol	9.9	g
d)	NaOH	0.1	g

DETD

e)	Pantoprazole Na .times. 1.5 H		

		403.0	g
f)	**Hydroxypropylmethylcellulose**		
		403.0	g
	2910 (USP)		
g)	Propylene glycol	201.5	g
h)	NaOH	1.0	g

DETD

c)	Pantoprazole Na .times. 1.5 H.sub.2 O		
		403.0	g
d)	Na carbonate	87.3	g
e)	Microcrystalline **cellulose**		
		117.0	g
	(Avicel PH101)		
f)	Na **carboxymethylcellulose**		
		18.0	g

DETD c)-f) are premixed dry and subsequently moistened to a paste-like consistency with a solution of Na carbonate and Na **carboxymethylcellulose** in water in a conventional kneader or high-speed mixer. The resulting composition is then extruded and shaped into pellets by. . .

CLM What is claimed is:

. . . An oral pharmaceutical composition as claimed in claim 3, wherein the intermediate layer contains, as water-insoluble, release-slowing film former, water-insoluble **cellulose** ether and/or polyvinyl acetate.

6. An oral pharmaceutical composition as claimed in claim 2, wherein the outer enteric layer comprises a **cellulose**-based coating.

7. An oral pharmaceutical composition as claimed in claim 6, wherein the **cellulose**-based coating is a member selected from the group consisting of a **carboxymethylethylcellulose, cellulose** acetate phthalate, **cellulose** acetate trimellitate, hydroxy-**propylmethylcellulose** phthalate and **hydroxypropylmethylcellulose** acetate succinate.

. . . penicillin G, penicillin V, ampicillin, mezlocillin, amoxicillin, bacitracin, polymyxin, tetracyline, chlorotetracycline, oxytetracycline, minocycline, doxycycline, imipenem, loracarbef, meropenem, panipenem, cefalexin, cefoxitin, **cefuroxime axetil**, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil, cephalothin, ciprofloxacin, norfloxacin, ofloxacin, pefloxacin and chloramphenicol.

. . . An oral pharmaceutical composition as claimed in claim 3, wherein the intermediate layer contains, as water-insoluble, release-slowing film former, ethyl **cellulose**, an ammonio methacrylate copolymer or polyvinyl alcohol.

IT 56-75-7, Chloramphenicol 57-62-5 57-92-1, Streptomycin, biological studies 59-87-0, Nitrofurazone 60-54-8, Tetracycline 61-33-6, Penicillin G, biological studies 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 69-53-4, Ampicillin 79-57-2, Oxytetracycline 87-08-1, Penicillin V 114-07-8, Erythromycin 153-61-7, Cephalothin 443-48-1, Metronidazole 564-25-0, Doxycycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 1405-87-4, Bacitracin 1406-11-7, Polymyxin 6506-37-2, Nimorazole 8063-07-8, Kanamycin 9002-89-5, Polyvinyl alcohol 9004-38-0, Cellulose acetate phthalate 9004-57-3, Ethyl cellulose 9050-31-1, Hydroxypropyl methyl cellulose phthalate 10118-90-8, Minocycline 13292-46-1, Rifampicin 14882-18-9, Bismuth subsalicylate 15686-71-2, Cefalexin 18323-44-9, Clindamycin 19387-91-8, Tinidazole 25086-15-1, Methacrylic acidmethyl methacrylate copolymer 26787-78-0, Amoxicillin 28572-98-7, Ethyl methacrylate-Methacrylic acid copolymer 33434-24-1, Eudragit RS 35607-66-0, Cefoxitin 37205-99-5, Carboxymethyl ethyl cellulose

37517-28-5, Amikacin 50370-12-2, Cefadroxil 51481-65-3, Mezlocillin 52907-01-4, Cellulose acetate trimellitate 53994-73-3, Cefaclor 57644-54-9, Bismuth subcitrate 63527-52-6, Cefotaxime 64221-86-9, Imipenem **64544-07-6**, Cefuroxime axetil 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 71138-97-1, Hydroxypropyl methyl cellulose acetate succinate 76470-66-1, Loracarbef 81103-11-9, Clarithromycin 82419-36-1, Ofloxacin 83905-01-5, Azithromycin 85721-33-1, Ciprofloxacin 87239-81-4, Cefpodoxime proxetil 87726-17-8, Panipenem 96036-03-2, Meropenem 102625-70-7, Pantoprazole 138786-67-1
(oral compns. contg. antimicrobial actives and sustained-release pantoprazole)

IT **64544-07-6**, Cefuroxime axetil
(oral compns. contg. antimicrobial actives and sustained-release pantoprazole)

L67 ANSWER 5 OF 13 USPATFULL
AN 1998:122082 USPATFULL
TI Biological agent compositions
IN Alakhov, Valery Yu., Ouebec, Canada
Kabanov, Alexander V., Omaha, NE, United States
Sveshnikov, Peter G., Moscow, Russian Federation
Severin, Eugenii S., Moscow, Russian Federation
PA Supratek Pharma, Inc., Montreal, Canada (non-U.S. corporation)
PI US 5817321 19981006
AI US 1995-478978 19950607 (8) <--
RLI Continuation-in-part of Ser. No. US 1995-374406, filed on 17 Jan 1995, now abandoned which is a continuation of Ser. No. US 1992-957998, filed on 8 Oct 1992, now abandoned
DT Utility
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Faulkner, D.
LREP Mathews, Collins, Shepherd & Gould, P.A.
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 1962
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to 1) pharmaceutical compositions and methods for chemotherapeutic agents and 2) pharmaceutical compositions for biological agents, particularly those whose target cells or tissues are resistant to the biological agent. The invention is targeted to overcome the resistance to biological agents that are developed by neoplasms and microbial infections. The formulation contains a biological agent and a polyether block copolymer. The block copolymer comprises an A-type linear polymeric segment joined at one end to a B-type linear polymeric segment; wherein the A type polymeric segment is hydrophilic, has repeating units which contribute an average Hansch-Leo fragmental constant of about 0.4 or less, and has a molecular weight contribution between 30 to about 500. The B-type segment is of relatively hydrophobic character, has repeating units which contribute an average Hansch-Leo fragmental constant of about -0.4 or more and a molecular weight contribution of about 30 to about 500, and has repeating units for each polymeric segment that comprise an ether linkage. The compositions may comprise chemotherapeutic agents, cytotoxic drugs, microbial treating agents, and a second biological agent.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1995-478978 19950607 (8) <--
DETD . . . intramuscularly, subcutaneously, intraperitoneally or intravenously. The compositions can be administered alone, or can be combined with a pharmaceutically-acceptable carrier or **excipient** according to standard pharmaceutical practice. For the oral mode of administration, the compositions can be used in the form of. . . syrups, elixirs, aqueous solutions and suspensions, and the like. In the case of tablets, carriers that can be used include **lactose**,

sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium **stearate**, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are **lactose** and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the compositions can be combined with. . . the art such as applicators or eye droppers. Such compositions can include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl **methylcellulose** or poly(vinyl alcohol), preservatives such as sorbic acid, EDTA or benzylchronium chloride, and the usual quantities of diluents and/or carriers.. . .

DETD . . . first generation cephalosporins such as cephapirin, cefaxolin, cephalexin, cephradine and cefadroxil; second generation cephalosporins such as cefamandole, cefoxitin, cefaclor, cefuroxime, **cefuroxime axetil**, cefonicid, cefotetan and ceforanide; third generation cephalosporins such as cefotaxime, ceftizoxime, ceftriaxone, cefoperazone and ceftazidime), tetracyclines (such as demeclocytetracycline, doxycycline,. . .

DETD . . . Chemicals, Germany) in octane. A reaction is initiated by adding a two-fold molar excess (with respect to the polypeptide) of **stearic acid** chloride in 0.2ml of 0.1M AOT.RTM. in octane to the mixture. The **stearic acid** chloride was obtained from staric acid (available from Reakhim, Russia) as described in Kabanov et al., Molek Biologiya (Russian), 22:. . . (Engl. edn.: 382-391), 1988. The reaction was conducted overnight at 25.degree. C. The product is precipitated three times with cold **acetone**, dissolved in RPMI 1640 medium and sterilely filtered through a 0.22 .mu.m filter. (The polyclonal antibody used in this experiment. . .

DETD The antibodies (Ab) to GFAP and .alpha.2-glycoprotein were modified with **stearic acid** residues as described in example 1. They were also covalently linked to Pluronic P85 as described by Kabanov et al.. . .

DETD . . . doxorubicin, (b) doxorubicin in 1% Pluronic P85, (c) doxorubicin in 10% Pluronic P85 containing 0.1 mg/ml of Ab modified with **stearic acid** chloride and (d) doxorubicin in 10% Pluronic P85 containing 0.1 mg/ml of Ab linked to Pluronic P85 were administered i.p.. . .

L67 ANSWER 6 OF 13 USPATFULL
AN 1998:65380 USPATFULL
TI Crystalline tazobactam, and its production and use
IN Trickes, Georg, Loerrach, Germany, Federal Republic of
PA Taiho Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 5763603 19980609
WO 9512601 19950511 <--
AI US 1995-403829 19950321 (8) <--
WO 1994-JP1855 19941102 <--
19950321 PCT 371 date
19950321 PCT 102(e) date
PRAI EP 1993-118016 19931106 <--
DT Utility
EXNAM Primary Examiner: Sham, Mukund J.; Assistant Examiner: Sripada, Pavanaram K.
LREP Sughrue, Mion, Zinn, Macpeak & Seas, PLLC
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 563
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Crystalline sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl) -methylpenam-3.alpha.-carboxylate-1,1-dioxide monohydrate (crystalline tazobactam sodium monohydrate) obtainable by adding to a concentrated aqueous solution of sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl)-methylpenam-3.alpha.-carboxylate-1,1-dioxide (tazobactam sodium) a solvent selected from **acetone** and ethanol in an amount corresponding to a solvent to water ratio of between about 95:5 and 99:1

v/v and crystallizing the desired product from the solvent mixture. The crystalline tazobactam sodium monohydrate exhibits a high .beta.-lactamase inhibitory activity in combination with .beta.-lactam antibiotics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5763603 19980609
WO 9512601 19950511 <--

AI US 1995-403829 19950321 (8) <--
WO 1994-JP1855 19941102 <--
19950321 PCT 371 date
19950321 PCT 102(e) date

PRAI EP 1993-118016 19931106 <--

AB . . . tazobactam sodium monohydrate) obtainable by adding to a concentrated aqueous solution of sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl)-methylpenam-3.alpha.-carboxylate-1,1-dioxide (tazobactam sodium) a solvent selected from **acetone** and ethanol in an amount corresponding to a solvent to water ratio of between about 95:5 and 99:1 v/v and. . .

SUMM . . . aqueous medium by a particular process which involves a careful balance between the water and one of the organic solvents **acetone** and ethanol. Thus the process of the present invention for producing crystalline sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl)-methylpenam-3.alpha.-carboxylate-1,1-dioxide monohydrate (crystalline tazobactam sodium monohydrate) is characterized by adding to a concentrated aqueous solution of sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl) -methylpenam-3.alpha.-carboxylate-1,1-dioxide (tazobactam sodium) a solvent selected from **acetone** and ethanol in an amount corresponding to a solvent to water ratio of between about 95:5 v/v and about 99:1. . .

SUMM The ratio of **acetone** or ethanol to water is critical. Already at a ratio of 9:1 v/v it is not possible to crystallize the. . .

SUMM The most preferable solvent is **acetone**. The **acetone**, in the amount dictated by the above recommended **acetone** to water ratio, can be added at once and the mixture be left for a sufficient time, e.g. about 10. . .

SUMM However, preferably the **acetone** to be added is divided in 3 volumes, which are added successively to the concentrated aqueous tazobactam solution a about room temperature. The first volume is about 23 to 27% of the total **acetone** volume, the second volume is about 24 to 28% of the total **acetone** volume and the third volume is about 46 to 52% of the total **acetone** volume preferably, the first volume is about 24 to 25% of the total **acetone** volume, the second volume is about 26to 27% of the total **acetone** volume and the third volume is about 48 to 50% of the total **acetone** volume. The first volume is preferably added together with a small volume of methanol so as to postpone crystallization until the addition of the second volume. To that end the methanol added to the first volume of **acetone** is preferably about 1 to 4% v/v of the **acetone** totally added. The second volume of **acetone** will start crystallization which can be promoted by scratching the wall of the vessel or by seeding with a small amount of tazobactam sodium monohydrate seed crystals. After addition of the third volume of **acetone** the crystal yield can be improved by cooling the mixture, e.g. to a temperature in the range of about -10.degree.. . .

SUMM . . . a sufficient time, e.g. about 1 to 30 hours, and afterwards isolated in conventional manner, e.g. by filtration, washed with **acetone** and dried at slightly elevated temperature, e.g. at about +25.degree. to +40.degree. C., preferably under reduced pressure.

SUMM Carriers useful in formulating the preparations are commonly used pharmaceutically acceptable non-toxic carriers such as gelatin, **lactose**, starch, magnesium **stearate**, talc, vegetable oil, animal oil, polyalkylene glycol, etc. The carrier may be used with other additives such as diluents, binders,. . .

SUMM . . . ceftazidime, cefoperazone, cefpimizole, cefpira,ide,

cefsulodin, cefoxitin, cefmetazole, latamoxef, cefotetan, cefbuperazone, cefminox, flomoxef, cephaloglycin, cephalexin, cefradine, cefatrizine, cefaclor, cefroxadine, cefadroxil, cefprozil, **cefuroxime axetil**, cefotiam hexetil, cefixime, cefteram pivoxil, cefpodoxime proxetil, ceftibuten, cefetamet pivoxil, cerdinir, cefcamate pivoxll, (6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-(azidomethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid or (E)-2-(isobutoxycarbonyl)-2-pentenyl (6R,7R)-7-[(Z)-2-(2-amino -4-thiazolyl)-2-(methoxyimino)acetamido]-3-(azidomethyl)-8-oxo-5-thia-1-azabicylo[4.2.0]oct-2-ene-2-carboxylate,. . .

DETD The viscous solution was diluted sequentially with 72 ml of methanol and 1000 ml of **acetone** at room temperature. The clear solution was transferred into a 6000 ml 4-neck vessel with mechanical stirrer and thermometer and diluted with 1080 ml of **acetone**. The solution became turbid, and a small amount of seed crystals was added. The mixture was stirred at room temperature overnight during which a white suspension was formed. This suspension was diluted over 3 hours with 2000 ml of **acetone**, gradually cooled to 5.degree. C. and stirred for A hours at this temperature. The crystals were collected by vacuum filtration on a glass funnel, washed in portions with 400 ml of **acetone**, dried in an oven under water jet vacuum at 30.degree. C. to constant weight. Yield: 361.4 g of sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl)-methylpenam-3.alpha.-carboxylate-1,1-dioxide. . .

DETD The concentrated solution was diluted with 340 ml of **acetone** at room temperature. Initially, two phases were formed; by stirring a white suspension was gradually formed. This was stirred for 21 hours at room temperature and filtered over a glass filter. The crystals were washed with 50 ml of **acetone** and dried in an oven under water jet vacuum at 30.degree. C. to constant weight. Yield 27.9 g of sodium. . .

DETD

Ampicillin	200 mg
Crystalline tazobactam sodium monohydride	200 mg
Lactose	100 mg
Crystalline **cellulose**	57 mg
Magnesium **stearate**	3 mg
Total	560 mg
	(amount per capsule)

DETD

Amoxicillin	100 mg
Crystalline tazobactam sodium monohydride	70 mg
Lactose	330 mg
Corn starch	490 mg
Hydroxypropyl methyl **cellulose**	10 mg
Total	1000 mg
	(amount per dose)

DETD

Bacampicillin	70 mg
Crystalline tazobactam sodium monohydride	70 mg
Lactose	33 mg
Crystalline **cellulose**	15 mg
Magnesium **stearate**	3 mg
Talc	4 mg
Corn starch	15 mg
Hydroxypropyl methyl **cellulose**	10 mg
Total	220 mg
	(amount per tablet)

DETD

Crystalline tazobactam sodium monohydride	120 mg
Hydroxypropyl **cellulose**	3 mg
Corn starch	25 mg
Magnesium **stearate**	2 mg
Total	150 mg
	(amount per tablet)

CLM What is claimed is:

. . . 2, which is obtainable by adding to a concentrated aqueous solution of sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl)--methylpenam-3.alpha.-carboxylate-1,1-dioxide (tazobactam sodium) a solvent selected from **acetone** and ethanol in an amount corresponding to a solvent to water ratio of between about 95:5 v/v and about 90:1. . .

. . . monohydrate) which is characterized by adding to a concentrated aqueous solution or sodium 2.alpha.-methyl-2.beta.-(1,2,3-triazol-1-yl)--methylpenam-3.alpha.-carboxylate-1,1-dioxide (tazobactam sodium) a solvent selected from **acetone** and ethanol in an amount corresponding to a solvent to water ratio of between about 95:5 v/v and about 99:1. . .

7. A process according to any one of claims 4 to 6, wherein the ratio of **acetone** or ethanol to water is in the range of about 96:4 to 98:2 v/v.

9. A process according to claim 4, wherein the solvent is **acetone**.

10. A process according to claim 9, wherein the **acetone** is added in 3 successive volumes at about room temperature, the first volume being about 23 to 27% of the total **acetone** volume, the second volume being about 24 to 28% of the total **acetone** volume and the third volume being about 46 to 52% of the total **acetone** volume.

11. A process according to claim 10, wherein the first volume is about 24 to 25% of the total **acetone** volume, the second volume is about 26 to 27% of the total **acetone** volume and the third volume is about 48 to 50% of the total **acetone** volume.

. . . 12. A process according to claim 10 or 11, wherein methanol amounting to about 1 to 4% v/v of the **acetone** totally added is added together with the first volume of **acetone**.

. . . ceftazidime, cefoperazone, cefpimizole, cefpiramide, cefsulodin, cefoxtin, cefmetazole, latamoxef, cefotetan, ceibuperazone, cefminox, flomoxef, cephaloglycin, cephalexin, cefradine, cefatizine, cefaclor, cefroxadine, cefadroxil, cefprozil, **cefuroxime axetil**, cefotiam hexetil, cefixime, cefteram pivoxil, cefpodoxime proxetil, ceftibuten, cefetamet pivoxil, cefdinir, cefcamate pivoxil, (6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)-acetamido]3-(azidomethyl)8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid or (E)2-(isobutoxy-carbonyl)-2-pentenyl (6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3(azidomethyl)-8oxo-5-thia-1-azabicyelo[4.2.0]oct-2-ene-2-carboxylate.

L67 ANSWER 7 OF 13 USPATFULL
AN 1998:19823 USPATFULL
TI Crystalline ceftiofur free acid
IN Dunn, Michael J., Paw Paw, MI, United States
Bergren, Michael S., Portage, MI, United States
Hardee, Gregory E., Kalamazoo, MI, United States
Shephard, Kenneth Paul, Kalamazoo, MI, United States
Chao, Robert S., Portage, MI, United States
Havens, Jeffrey L., Mattawan, MI, United States

PA Pharmacia & Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)
PI US 5721359 19980224
WO 9420505 19940915 <--
AI US 1995-549821 19950911 (8) <--
WO 1994-US1862 19940307 <--
19950911 PCT 371 date
19950911 PCT 102(e) date
RLI Continuation-in-part of Ser. No. US 1993-33291, filed on 12 Mar 1993, now abandoned
DT Utility
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Sripada, Pavanaram K.
LREP Gammill, Martha A.
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 957
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Anhydrous and crystalline free acid form of the cephalosporin antiobiotic ceftiofur, processes for its manufacture, and pharmaceutical composition containing it are provided. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5721359 19980224
WO 9420505 19940915 <--
AI US 1995-549821 19950911 (8) <--
WO 1994-US1862 19940307 <--
19950911 PCT 371 date
19950911 PCT 102(e) date

SUMM Many cephalosporin compounds, derivatives thereof, and processes for their preparation, are known. For example, the following are known: amorphous **cefuroxime axetil**, its crystalline sodium salt, its naphthyridine derivative and its sesquihydrate (U.S. Pat. Nos. 4,820,833; 4,298,732; 4,442,101); crystalline sodium cephemcarboxylate (U.S.. . .

SUMM By "pharmaceutically acceptable carrier or **excipient**" is meant any carrier or **excipient** that is commonly used in pharmaceutical compositions and are well known and readily prepared by one of ordinary skill in the art. Such carrier or **excipient** may be a solid or liquid and contain one or more suspending, dispersing, stabilizing, emulsifying, buffering, thickening, sweetening, flavoring, coloring. . .

SUMM . . . Pat. No. 4,902,683. In one readily used method, once the hydrochloride salt is obtained by adding hydrochloric acid to a water/ **acetone** solution of ceftiofur, the resulting solution is cooled slowly to obtain crystalline ceftiofur hydrochloride.

SUMM . . . herein, with any of several different organic/aqueous solutions, including 1:1 solutions of water with a water miscible solvent, such as **acetone**, acetonitrile, methanol, tetrahydrofuran (THF) or isopropanol, or a 3:7 solution of water with a water miscible solvent, such as ethanol.. . .

SUMM . . . dosage unit forms are selected from the group consisting of lipids, carbohydrates, proteins and mineral solids, for example, starch, sucrose, **lactose**, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch, talc and the like. Liquid preparations are prepared in water or aqueous vehicles which advantageously contain suspending agents, for example, **methylcellulose**, alginates, tragacanth, pectin, kelgin, cartagenan, acacia, polyvinylpyrrolidone, polyvinyl alcohol, and the like, to increase the viscosity of the composition. Additionally. . . cobalt 60 irradiation, or by exposure to a sterilizing gas, for example, ethylene oxide. The aforesaid carriers, vehicles, diluents, surfactants, **excipients**, preservatives, isotonic agents and the like constitute the pharmaceutical means which adapt the preparations for systemic administration.

DETD . . . ml of ethanol. This slurry is filtered and washed with diethyl ether. The solids are dissolved in 835 ml of **acetone** and 1567 ml of ethanol. This solution is concentrated under vacuum to a volume of 167 ml. This slurry is. . .

CLM What is claimed:
4. The composition of claim 3 which further comprises a pharmaceutically acceptable carrier or **excipient**.

8. The composition of claim 7 which further comprises a pharmaceutically acceptable carrier or **excipient**.

16. The process of claim 15 wherein the solvent is selected from the group consisting of **acetone**, tetrahydrofuran (THF), and ethanol.

IT 64-17-5, Ethanol, uses **67-64-1**, Acetone, uses 109-99-9, THF, uses
(prepn. of cryst. ceftiofur and sustained-release compns.)
IT **67-64-1**, Acetone, uses
(prepn. of cryst. ceftiofur and sustained-release compns.)

L67 ANSWER 8 OF 13 USPATFULL
AN 97:25135 USPATFULL
TI Diastereomers of 1-(isopropoxycarbonyloxy)ethyl 3-cephem-4-carboxylate and processes for their preparation
IN Fischer, Gerd, Limburg, Germany, Federal Republic of
Defo.beta.a, Elisabeth, Idstein, Germany, Federal Republic of
Gerlach, Uwe, Frankfurt am Main, Germany, Federal Republic of
H orlein, Rolf, Frankfurt am Main, Germany, Federal Republic of
Krass, Norbert, Frankfurt am Main, Germany, Federal Republic of
Lattrell, Rudolf, K onigstein/Taunus, Germany, Federal Republic of
Stache, Ulrich, Hofheim am Taunus, Germany, Federal Republic of
Wollmann, Theodor, Hofheim am Taunus, Germany, Federal Republic of
Isert, Dieter, Eschborn, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5614623 19970325 <--
AI US 1995-447249 19950522 (8) <--
RLI Division of Ser. No. US 1992-940367, filed on 3 Sep 1992, now patented, Pat. No. US 5461043
PRAI DE 1991-4129771 19910907 <--
DT Utility
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Sripada, Pavanaram K.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 517
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Enterally absorbable diastereomers of 1-(isopropoxycarbonyloxy)ethyl (6R, 7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-(methoxymethyl)-3-cephem-4-carboxylate of the formula I ##STR1## and their physiologically acceptable salts and also diastereomerically pure salts of the compounds of the formula II ##STR2## where HX is a mono- or polybasic acid and where X is an inorganic or organic physiologically acceptable anion, and a process for the preparation of these compounds of the formula I or II, which comprises first precipitating the more sparingly soluble diastereomer of the formula IV in the mixing together of 1 equivalent of a solution of the diastereomer mixture of the formula III with 0.2-2 equivalents of a solution of the acid component HY and separating it off by filtration, then precipitating the more readily soluble diastereomer of the formula IV from the filtration solution, it being possible for the acid component HY to be identical or different in the consecutive steps.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5614623 19970325 <--
AI US 1995-447249 19950522 (8) <--
PRAI DE 1991-4129771 19910907 <--
SUMM . . . mixtures of diastereomers also exist, for example, in the case of cefotiam hexetil (Drugs of the Future 13, 230 (1988)), **cefuroxime axetil** (Drugs of the Future 10, 112 (1985)), baccefuzonam (N.A. Kuck et al., Proc. 14th Int. Congr. Chemother. 2, 1137 (1985)). . .
SUMM . . . their mixtures. Preferred solvents are, for example, benzene, toluene, ethyl acetate, butyl acetate, methanol, ethanol, n-propanol, isopropanol, tert-butanol, diisopropyl ether, **acetone**, acetonitrile and dichloromethane and mixtures thereof.
SUMM The oral preparations can contain the customary **excipients** and/or diluents. Thus, for example, for capsules or tablets binders, such as, for example, gelatine, sorbitol, polyvinylpyrrolidone or **carboxymethylcellulose**, diluents, such as, for example, **lactose**, sugar, starch, calcium phosphates or polyethylene glycol, lubricants, such as, for example, talc or magnesium **stearate**, are possible. For liquid preparations, for example aqueous or oily suspensions, syrups or similar known preparation forms are suitable.

L67 ANSWER 9 OF 13 USPATFULL
AN 96:77883 USPATFULL
TI Diastereomers of 1-(isopropoxycarbonyloxy) ethyl 3-cephem 4-carboxylate
IN Fischer, Gerd, Limburg, Germany, Federal Republic of
Defossa, Elisabeth, Idstein, Germany, Federal Republic of
Gerlach, Uwe, Frankfurt, Germany, Federal Republic of
H orlein, Rolf, Frankfurt am Main, Germany, Federal Republic of
Krass, Norbert, Frankfurt am Main, Germany, Federal Republic of
Lattrell, Rudolf, K onigstein/Taunus, Germany, Federal Republic of
Stache, Ulrich, Hofheim am Taunus, Germany, Federal Republic of
Wollmann, Theodor, Hofheim am Taunus, Germany, Federal Republic of
Isert, Dieter, Eschborn, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5550232 19960827 <--
AI US 1995-447229 19950522 (8) <--
RLI Division of Ser. No. US 1992-940367, filed on 3 Sep 1992, now patented, Pat. No. US 5461043
PRAI DE 1991-4129771 19910907 <--
DT Utility
EXNAM Primary Examiner: Rizzo, Nicholas
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 494
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Enterally absorbable diastereomers of 1-(isopropoxycarbonyloxy)ethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-(methoxymethyl)-3-cephem-4-carboxylate of the formula I ##STR1## and their physiologically acceptable salts and also diastereomerically pure salts of the compounds of the formula II ##STR2## where HX is a mono- or polybasic acid and where X is an inorganic or organic physiologically acceptable anion, and a process for the preparation of these compounds of the formula I or II, which comprises first precipitating the more sparingly soluble diastereomer of the formula IV in the mixing together of 1 equivalent of a solution of the diastereomer mixture of the formula III with 0.2-2 equivalents of a solution of the acid component HY and separating it off by filtration, then precipitating the more readily soluble diastereomer of the formula IV from the filtration solution, it being possible for the acid component HY to be identical or different in the consecutive partial steps and any desired sequence of addition of

different acid components HY being possible, and optionally further purifying the obtained salts by crystallization, are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5550232 19960827 <--
AI US 1995-447229 19950522 (8) <--
PRAI DE 1991-4129771 19910907 <--
SUMM . . . mixtures of diastereomers also exist, for example, in the case of cefotiam hexetil (Drugs of the Future 13, 230 (1988)), **cefuroxime axetil** (Drugs of the Future 10, 112 (1985)), baccefuzonam (N. A. Kuck et al., Proc. 14th Int. Congr. Chemother. 2, 1137. . .
SUMM . . . their mixtures. Preferred solvents are, for example, benzene, toluene, ethyl acetate, butyl acetate, methanol, ethanol, n-propanol, isopropanol, tert-butanol, diisopropyl ether, **acetone**, acetonitrile and dichloromethane and mixtures thereof.
SUMM The oral preparations can contain the customary **excipients** and/or diluents. Thus, for example, for capsules or tablets binders, such as, for example, gelatine, sorbitol, polyvinylpyrrolidone or **carboxymethylcellulose**, diluents, such as, for example, **lactose**, sugar, starch, calcium phosphates or polyethylene glycol, lubricants, such as, for example, talc or magnesium **stearate**, are possible. For liquid preparations, for example aqueous or oily suspensions, syrups or similar known preparation forms are suitable.

L67 ANSWER 10 OF 13 USPATFULL
AN 95:94909 USPATFULL
TI Diastereomers of 1-(isopropoxycarbonyloxy)ethyl 3-cephem-4-carboxylate
IN Fischer, Gerd, Limburg, Germany, Federal Republic of
Defossa, Elisabeth, Idstein, Germany, Federal Republic of
Gerlach, Uwe, Frankfurt am Main, Germany, Federal Republic of
Horlein, Rolf, Frankfurt am Main, Germany, Federal Republic of
Krass, Norbert, Frankfurt am Main, Germany, Federal Republic of
Lattrell, Rudolf, Konigstein/Taunus, Germany, Federal Republic of
Stache, Ulrich, Hofheim am Taunus, Germany, Federal Republic of
Wollmann, Theodor, Hofheim am Taunus, Germany, Federal Republic of
Isert, Dieter, Eschborn, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5461043 19951024 <--
AI US 1992-940367 19920903 (7) <--
PRAI DE 1991-4129771 19910907 <--
DT Utility
EXNAM Primary Examiner: Rizzo, Nicholas
LREP Finnegan, Henderson, Farabow, Garrett & Dunner
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 518
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Enterally absorbable diastereomers of 1-(isopropoxycarbonyloxy)ethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-(methoxymethyl)-3-cephem-4-carboxylate of the formula I ##STR1## and their physiologically acceptable salts and also diastereomerically pure salts of the compounds of the formula II ##STR2## where HX is a mono- or polybasic acid and where X is an inorganic or organic physiologically acceptable anion, and a process for the preparation of these compounds of the formula I or II, which comprises first precipitating the more sparingly soluble diastereomer of the formula IV in the mixing together of 1 equivalent of a solution of the diastereomer mixture of the formula III with 0.2-2 equivalents of a solution of the acid component HY and separating it off by filtration, then precipitating the more readily soluble diastereomer of the formula IV from the filtration solution, it being possible for the acid component HY to be identical or different in the consecutive partial steps and any desired sequence of addition of

different acid components HY being possible, and optionally further purifying the obtained salts by crystallization, are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5461043 19951024 <--
AI US 1992-940367 19920903 (7) <--
PRAI DE 1991-4129771 19910907 <--
SUMM . . . mixtures of diastereomers also exist, for example, in the case of cefotiam hexetil (Drugs of the Future 13, 230 (1988)), **cefuroxime axetil** (Drugs of the Future 10, 112 (1985)), baccefuzonam (N. A. Kuck et al., Proc. 14th Int. Congr. Chemother. 2, 1137. . .
SUMM . . . their mixtures. Preferred solvents are, for example, benzene, toluene, ethyl acetate, butyl acetate, methanol, ethanol, n-propanol, isopropanol, tert-butanol, diisopropyl ether, **acetone**, acetonitrile and dichloromethane and mixtures thereof.
SUMM The oral preparations can contain the customary **excipients** and/or diluents. Thus, for example, for capsules or tablets binders, such as, for example, gelatine, sorbitol, polyvinylpyrrolidone or **carboxymethylcellulose**, diluents, such as, for example, **lactose**, sugar, starch, calcium phosphates or polyethylene glycol, lubricants, such as, for example, talc or magnesium **stearate**, are possible. For liquid preparations, for example aqueous or oily suspensions, syrups or similar known preparation forms are suitable.

L67 ANSWER 11 OF 13 USPATFULL
AN 95:36392 USPATFULL
TI Topical treatment of acne with cephalosporins
IN Robinson, Howard N., Lutherville, MD, United States
Martin, Neil F., Potomac, MD, United States
PA Towsend, Marvin S., Towson, MD, United States (part interest)
Bloom, Leonard, Rockville, MD, United States (part interest) a part interest to each
PI US 5409917 19950425 <--
AI US 1993-126799 19930924 (8) <--
RLI Continuation-in-part of Ser. No. US 1992-883914, filed on 12 May 1992, now patented, Pat. No. US 5260292 which is a continuation-in-part of Ser. No. US 1991-664795, filed on 5 Mar 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Kishore, Gollamudi S.
LREP Bloom, Leonard; Towsend, Marvin S.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4043
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and composition for topically treating acne and acneiform dermal disorders includes applying an amount of a cephalosporin antibiotic effective to treat the acne and acneiform dermal disorders. The antibiotic is blended with a carrier suitable for topical application to dermal tissues. The carrier is selected from the group consisting of an aqueous liquid, an alcohol base, a water soluble gel, a lotion, an ointment, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petrolatum, liposomes, a time-release patch, and a liquid-absorbed wipe. The cephalosporin can also be combined with benzoyl peroxide in a gel carrier.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5409917 19950425 <--
AI US 1993-126799 19930924 (8) <--
SUMM . . . cefuroxime, cephalexin, cephalosporin C cephalosporin C, sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime-axetil**), dihydratecephalothin, and moxalactam.
DETD . . . cephalothin; cephapirin; cephradine; cefaclor; cefamandole;

cefonicid; ceforanide; cefotetan (a cephamycin); cefoxitin (a cephamycin); cefuroxime; the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime axetil** and **Ceftin**); cefoperazone; cefotaxime; cefpodoxime proxetil, ceftazidime; ceftizoxime; ceftriaxone; moxalactam (a 1-oxa-beta-lactam); and loracarbef (lorabid), among others.

DETD . . . Weight Per Cent of ingredient in overall lotion

Ingredient	
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cefaclor	3.00

DETD . . . contain only cefaclor for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cefaclor. Then, the contents of Container A and Container B are combined. . .

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefaclor	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	

	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefaclor	3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefaclor	3

DETD . . . Weight Per Cent of ingredient in overall lotion

Ingredient	
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cefuroxime	3.00

DETD . . . contain only cefuroxime for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cefuroxime. Then, the contents of Container A and Container B are combined. . .

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	

	5
Butylated hydroxyanisole	
	0.10
Polyoxyl 40 **stearate**	
	0.25
Water, deionized or distilled	
	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	
	5
Acetone	10
Dioctyl sodium sulphosuccinate	
	0.1
cefuroxime	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	
	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	
	5
Butylated hydroxyanisole	
	0.10
Polyoxyl 40 **stearate**	
	0.25
Water, deionized or distilled	
	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	
	5
Acetone	10
Dioctyl sodium sulphosuccinate	
	0.1
cefuroxime	3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	
	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	
	0.10
Polyoxyl 40 **stearate**	
	0.25
Water, deionized or distilled	
	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	
	5
Acetone	10
Dioctyl sodium sulphosuccinate	
	0.1
cefuroxime	3

DETD A topical dermatological composition containing **cefuroxime-axetil** is obtained as follows. Mix the following ingredients in the amounts specified.

DETD

Ingredient	Weight Per Cent
Ethyl alcohol	41.5
Laureth-4	0.5

Isopropyl alcohol
6.0
cefuroxime-axetil
2.0
Purified water balance

DETD The composition in this example contains approximately 2% **cefuroxime-axetil**. Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

DETD A topical dermatological composition containing **cefuroxime-axetil** is obtained as follows. Mix the following ingredients in the amounts specified.

DETD

Ingredient	Weight Per Cent
Ethyl alcohol	71.2
Propylene glycol	26.8
cefuroxime-axetil	2.0

DETD The composition in this example contains approximately 2% **cefuroxime-axetil**.

DETD A 30 kilogram batch of a composition of the present invention containing **cefuroxime-axetil** (as 0.75% by weight) is prepared as follows. 180 grams of Carbopol 940.TM. (0.6% by weight of the final weight. . . propyl paraben (0.02% by weight of the final weight of the composition). The mixture is added to 225 grams of **cefuroxime-axetil** dispersed in 11.4 liters of distilled water maintained at 50 degrees Centigrade. Parts A and B are then mixed thoroughly. . . are thoroughly mixed into a viscous gel. Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 2%, 3%, 4%, 5%, and 10%.

DETD . . . the following ingredients in suitable amounts: allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene glycol, sodium hydroxide, purified water and **cefuroxime-axetil** .

DETD

Ingredient	Weight Per Cent
Benzoyl peroxide (micronized)	1 to 35
Calcium phosphate	63 to 98.5
cefuroxime-axetil	0.5 to 5

DETD

Ingredient	Weight Per Cent
cefuroxime-axetil	0.5 to 5
Benzoyl peroxide (micronized)	1 to 30
Ethanol	The Balance to 100%

DETD A topical dermatological composition containing **cefuroxime-axetil** is obtained as follows. Mix the following ingredients in the amounts specified.

DETD

Ingredient	Weight Per Cent
Ethyl alcohol	48.0
Laureth-4	0.5
Isopropyl alcohol	4.0

Propylene glycol
10.0
cefuroxime-axetil
1.0
Purified water balance

DETD The composition in this example contains approximately 1% **cefuroxime-axetil**. Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

DETD A topical dermatological gel composition containing **cefuroxime-axetil** antibiotic and benzoyl peroxide in a gel carrier or vehicle is obtained as follows.

DETD . . . 5 grams of benzoyl peroxide and approximately 89 grams of gel carrier or vehicle). To a second container add powdered **cefuroxime-axetil** (approximately 3 grams of **cefuroxime-axetil**). The contents of the first container and the contents of the second container are stable for long periods of time. When the topical composition containing **cefuroxime-axetil** and benzoyl peroxide of the invention is to be made, a quantity of 70% ethyl alcohol (e. g. 3 ml.) is added to the second container to dissolve the **cefuroxime-axetil** and form an alcoholic solution thereof. Then the alcoholic solution of **cefuroxime-axetil** is added to the first container, and all the ingredients are mixed to form the topical gel composition of the invention which contains both **cefuroxime-axetil** and benzoyl peroxide. This composition of the invention is stable, under refrigeration, for approximately 3 months.

DETD More specifically, the blended topical gel composition of the invention with contains **cefuroxime-axetil** and benzoyl peroxide in a gel carrier or vehicle has the following components in the approximate amounts specified.

DETD

Ingredient	Weight Per Cent
cefuroxime-axetil	3.0
Benzoyl peroxide	5.0
Gel carrier or vehicle	92.0

DETD The composition in this example contains approximately 3% **cefuroxime-axetil**. Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

DETD A dermatological lotion containing **cefuroxime-axetil** is obtained by mixing the following ingredients in the amounts specified. The ingredients in Container A is blended with the. . .

DETD . . . Weight Per Cent of ingredient in overall lotion

Ingredient	
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
P01yoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80

Propylene glycol 3.00
Acetone 7.00
Dioctyl sodium sulfosuccinate 0.10
In Container B:
Acetone 3.00
cefuroxime-axetil 3.00

DETD Container B can contain only **cefuroxime-axetil** for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the **cefuroxime-axetil**. Then, the contents of Container A and Container B are combined to form the complete lotion composition of the invention.

DETD The composition in this example contains approximately 3% **cefuroxime-axetil**. Other suitable compositions can be made in accordance with Example 62 which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefuroxime-axetil	2

DETD Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefuroxime-axetil	3

DETD Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefuroxime-axetil	3

DETD Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

DETD

. . . or distilled	51.65
Butylated hydroxyanisole	0.10
Benzoyl peroxide (micronized)	5
Dioctyl sodium sulphosuccinate	1
Colloidal Bentonite	2.5
Carboxy vinyl polymer (acid form)	1
Ethyl alcohol	35
Diisopropanolamine	0.75
cefuroxime-axetil	3

DETD Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

DETD

. . . or distilled	54.97
Butylated hydroxyanisole	0.10
Benzoyl peroxide (micronized)	5
Dioctyl sodium sulphosuccinate	1
Colloidal Bentonite	1.5
Carboxy vinyl polymer (acid form)	0.25
Ethyl alcohol	35
Diisopropanolamine	0.18
cefuroxime-axetil	2

DETD Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

DETD An oil-in-water emulsion containing **cefuroxime-axetil** in ointment form is obtained as follows.

DETD Part A is comprised of a 3.33% aqueous solution of **cefuroxime-**

axetil.

DETD . . . A is mixed with 40 ml. of Part B to provide an oil-in-water emulsion in ointment form containing approximately 2% **cefuroxime -axetil**. Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

DETD A mineral-oil-based **cefuroxime-axetil** ointment is obtained as follows.

DETD Part A is comprised of a 6.66% aqueous solution of **cefuroxime-axetil**.

DETD . . . Mix 30 ml. of Part A with 70 ml. of Part B to provide a mineral-oil-based ointment containing approximately 2% **cefuroxime-axetil**. Other suitable compositions can be made in accordance with this example which include **cefuroxime-axetil** in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

DETD

Ingredient	Weight Percent of ingredient in overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cefotetan	3.00

DETD . . . contain only cefotetan for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cefotetan. Then, the contents of Container A and Container B are combined. . .

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefotetan	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefotetan	3

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefotetan	3

DETD

Ingredient	Weight Percent of ingredient in overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cephalexin	3.00

DETD . . . contain only cephalexin for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone**

are added to Container B to dissolve the cephalexin. Then, the contents of Container A and Container B are combined. . .

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cephalexin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cephalexin	3

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cephalexin	3

DETD

Ingredient	Weight Percent of ingredient in overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cephalothin	3.00

DETD . . . contain only cephalothin for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cephalothin. Then, the contents of Container A and Container B are combined. . .

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cephalothin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3

Benzoyl peroxide (micronized) 5
Acetone 10
Dioctyl sodium sulphosuccinate 0.1
cephalothin 3

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cephalothin	3

DETD

Ingredient	Weight Percent of ingredient in overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cephalosporin C	3.00

DETD . . . only cephalosporin C for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cephalosporin C. Then, the contents of Container A and Container B are. . .

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10

Polyoxyl 40 **stearate**
0.25
Water, deionized or distilled
66.8
Propylene glycol 3
Benzoyl peroxide (micronized)
5
Acetone 10
Dioctyl sodium sulphosuccinate
0.1
cephalosporin C 2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cephalosporin C	3

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cephalosporin C	3

DETD

Ingredient	Weight Percent of ingredient in overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	

0.10
Polyoxyl 40 **stearate**
0.25
Water, deionized or distilled
70.80
Propylene glycol 3.00
Acetone 7.00
Dioctyl sodium sulfosuccinate
0.10
In Container B:
Acetone 3.00
cefoperazone 3.00

DETD . . . contain only cefoperazone for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cefoperazone. Then, the contents of Container A and Container B are combined. . .

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefoperazone	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefoperazone	3

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15

Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefoperazone	3

DETD . . . Weight Per Cent of ingredient in Ingredient overall lotion

In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cefotaxime	3.00

DETD . . . contain only cefotaxime for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cefotaxime. Then, the contents of Container A and Container B are combined. . .

DETD Ingredient Weight Per Cent

Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefotaxime	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefotaxime	3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
cefotaxime	3

DETD . . . 7 minutes to give a dispersion of liposomes (multilamellar vesicles, MLV). The dispersion is frozen by the used of dry ice/**acetone** and dried by vacuum lyophilization. The powder obtained is collected and placed in a tube for centrifugal separation. A solution. . .

DETD The detailed examples set forth above employ the following cephalosporins: cefaclor; cefoperazone; cefotaxime; cefotetan; cefuroxime; cephalexin; cephalosporin C; cephalothin; and **cefuroxime-axetil**.

DETD . . . cefuroxime; cephalexin; cephalosporin C; cephalosporin C, sodium salt; cephalothin; cephalothin, sodium salt; cephapirin; cephradine; the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime-axetil**); dihydratecephalothin; moxalactam; and loracarbef.

CLM What is claimed is:

. . . cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime-axetil**), dihydratecephalothin, moxalactam, and loracarbef and a pharmaceutical carrier, applied directly to affected dermal tissues, effective to treat the acne wherein. . .

. . . cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime-**

axetil), dihydratecephalothin, moxalactam, and loracarbef, wherein said cephalosporin antibiotic is applied directly to affected dermal tissues in an amount effective to. . .
. . . cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime-axetil**), dihydratecephalothin, moxalactam, and loracarbef effective to treat the acne, and a pharmaceutical carrier, wherein said pharmaceutical carrier is a mixture. . .
. . . cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime-axetil**), dihydratecephalothin, moxalactam, and loracarbef and a pharmaceutical carrier, effective to treat the acne, wherein the antibiotic is present in a. . .

IT 57-55-6, Propylene glycol, biological studies 58-71-9, Cephalothin sodium 61-24-5, Cephalosporin C 64-17-5, Ethanol, biological studies 67-63-0, Isopropanol, biological studies 94-36-0, Benzoyl peroxide, biological studies 153-61-7, Cephalothin 9002-92-0, Laureth 11111-12-9, Cephalosporin 15686-71-2, Cephalexin 21593-23-7, Cephapirin 25953-19-9, Cefazolin 35607-66-0, Cefoxitin 38821-53-3, Cephradine 42540-40-9, Cefamandole nafate 50370-12-2, Cefadroxil 53994-73-3, Cefaclor 55268-75-2, Cefuroxime 56796-20-4, Cefmetazole 60925-61-3, Ceforanide 61270-58-4, Cefonicid 62893-19-0, Cefoperazone 63527-52-6, Cefotaxime **64544-07-6**, Cefuroxime axetil 64952-97-2, Moxalactam 68401-81-0, Ceftizoxime 69712-56-7, Cefotetan 72558-82-8, Ceftazidime 73384-59-5, Ceftriaxone 74970-31-3, Cephalosporin C sodium 76470-66-1, Loracarbef 79350-37-1, Cefixime 87239-81-4, Cefpodoxime proxetil
(topical treatment of acne with cephalosporins)

IT **64544-07-6**, Cefuroxime axetil
(topical treatment of acne with cephalosporins)

L67 ANSWER 12 OF 13 USPATFULL
AN 93:93782 USPATFULL
TI Topical treatment of acne with aminopenicillins
IN Robinson, Howard N., Lutherville, MD, United States
Martin, Neil F., Potomac, MD, United States
PA Towsend, Marvin S., Rockville, MD, United States (part interest)
Bloom, Leonard, Towson, MD, United States (part interest) part interest to each
PI US 5260292 19931109 <--
AI US 1992-883914 19920512 (7) <--
RLI Continuation-in-part of Ser. No. US 1991-664795, filed on 5 Mar 1991, now abandoned
DT Utility
EXNAM Primary Examiner: Page, Thurman H.; Assistant Examiner: Kishore, G. S.
LREP Bloom, Leonard; Towsend, Marvin S.
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2653
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and composition for topically treating acne and acneiform dermal disorders includes applying an amount of an antibiotic selected from the group consisting of ampicillin, amoxicillin, other aminopenicillins, and cephalosporin, and derivatives and analogs thereof, effective to treat the acne and acneiform dermal disorders. The antibiotic is blended with a carrier suitable for topical application to dermal tissues. The carrier is selected from the group consisting of an aqueous liquid, an alcohol base, a water soluble gel, a lotion, an ointment base, petrolatum, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petrolatum, a suspension of solid particles in a liquid, and a suspension of an ion-exchange resin in water.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5260292 19931109 <--
AI US 1992-883914 19920512 (7) <--
SUMM . . . cephalothin, cephapirin, cephradine, cefaclor, cefamandole, cefonicid, ceforanide, cefotetan (a cephamycin), cefoxitin (a cephamycin), cefuroxime, the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime axetil**), cefoperazone, cefotaxime, ceftazidime, **ceftin**, ceftizoxime, ceftriaxone, and moxalactam (a 1-oxa-beta-lactam).
DETD . . . and Toricelocin); cephapirin sodium; cefadroxil; cefazolin; cephalexin; cephalothin; cephapirin; cephradine; cefaclor; cefamandole; cefonicid; ceforanide; cefotetan (a cephamycin); cefoxitin (a cephamycin); **ceftin**; cefuroxime; the 1-acetyloxy ethyl ester of cefuroxime (**cefuroxime axetil**); cefoperazone; cefotaxime; ceftazidime; ceftizoxime; ceftriaxone; and moxalactam (a 1-oxa-beta-lactam).

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	71.8
Propylene glycol	3
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	71.8
Propylene glycol	3
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	

	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	3

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10

Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	3

DETD

Ingredient	Weight Percent of ingredient in overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
ampicillin	3.00

DETD . . . contain only ampicillin for a long period of time. Just prior to forming the complete location composition, 3 grams of **acetone** are added to Container B to dissolve the ampicillin. Then, the contents of Container A and Container B are combined. . .

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Cephalosporin C	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30

Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Cephalosporin C	3

DETD A topical dermatological composition containing **ceftin** is obtained as follows.

DETD

Ingredient	Weight Percent
Ethyl alcohol	44.0
Laureth-4	0.5
Isopropyl alcohol	6.0
Ceftin	1.0
Purified water	balance

DETD The composition in Example 38 contains approximately 1% **Ceftin** .

DETD Other suitable compositions can be made in accordance with Example 38 which include **Ceftin** in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%. Example 37

DETD A topical dermatological composition containing **cefuroxime axetil** is obtained as follows. It is noted that **cefuroxime axetil** is th 1-acetyloxy ethyl ester of cefuroxime.

DETD

Ingredient	Weight Percent
Ethyl alcohol	44.0
Laureth-4	0.5
Isopropyl alcohol	6.0
Cefuroxime axetil	1.0
Purified water	balance

DETD The composition in Example 50 contains approximately 1% **Cefuroxime axetil.**

DETD Other suitable compositions can be made in accordance with Example 50 which include **Cefuroxime axetil** in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

DETD A topical dermatological composition containing **cefuroxime axetil** is obtained as follows. Mix the following ingredients in the amounts specified.

DETD

Ingredient	Weight Percent
Ethyl alcohol	48.0
Laureth-4	0.5
Isopropyl alcohol	4.0
Propylene glycol	10.0
Cefuroxime axetil	1.0
Purified water	balance

DETD The composition in Example 51 contains approximately 1% **Cefuroxime axetil.**

DETD Other suitable compositions can be made in accordance with Example 51 which include **Cefuroxime axetil** in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

DETD A topical dermatological composition containing **ceftin** is obtained as follows.

DETD

Ingredient	Weight Percent
Ethyl alcohol	44.0
Laureth-4	0.5
Isopropyl alcohol	6.0
Ceftin	1.0
Purified water	balance

DETD The composition in Example 56 contains approximately 1% **Ceftin** .

DETD Other suitable compositions can be made in accordance with Example 56 which include **Ceftin** in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

DETD A topical dermatological composition containing **ceftin** is obtained as follows.

DETD

Ingredient	Weight Percent
Ethyl alcohol	48.0
Laureth-4	0.5
Isopropyl alcohol	4.0
Propylene glycol	10.0
Ceftin	1.0
Purified water	balance

DETD The composition in Example 57 contains approximately 1% **Ceftin** .

DETD Other suitable compositions can be made in accordance with Example 57 which include **Ceftin** in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

DETD

Ingredient	Weight Percent of ingredient in overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
amoxicillin	3.00

DETD . . . contain only amoxicillin for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the amoxicillin. Then, the contents of Container A and Container B are combined. . .

DETD

	Weight Percent of ingredient in

Ingredient	overall lotion
In Container A:	
Ethoxylated cetyl-stearyl alcohol	7.00
Cetyl alcohol	0.75
Isopropyl myristate	5.00
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	70.80
Propylene glycol	3.00
Acetone	7.00
Dioctyl sodium sulfosuccinate	0.10
In Container B:	
Acetone	3.00
cephalosporin C	3.00

DETD . . . only cephalosporin C for a long period of time. Just prior to forming the complete lotion composition, 3 grams of **acetone** are added to Container B to dissolve the cephalosporin C. Then, the contents of Container A and Container B are. . .

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	71.8
Propylene glycol	3
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	71.8
Propylene glycol	3
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7

Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	2

DETD

Ingredient	Weight Percent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	71.8
Propylene glycol	3
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	

	0.25
Water, deionized or distilled	71.8
Propylene glycol	3
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8

Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Amoxicillin	3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	

5
Acetone 10
Dioctyl sodium sulphosuccinate
0.1
Amoxicillin 3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Cephalosporin C	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Cephalosporin C	2

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Isostearyl neopentanoate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5

Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Cephalosporin C	3

DETD

Ingredient	Weight Per Cent
Ethoxylated cetyl-stearyl alcohol	15
Cetyl alcohol	1.25
Decyl oleate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 **stearate**	0.25
Water, deionized or distilled	57.30
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Cephalosporin C	3

IT 58-71-9, Cephalothin sodium salt 61-24-5, Cephalosporin C 69-52-3, Ampicillin sodium salt 69-53-4, Ampicillin 153-61-7, Cephalothin 1406-05-9, Penicillin 3485-14-1, Cyclacillin 7177-48-2, Ampicillin trihydrate 11111-12-9, Cephalosporin 15686-71-2, Cephalexin 19379-33-0, L(+) Ampicillin 21593-23-7, Cephapirin 23277-71-6, Ampicillin potassium salt 24356-60-3, Cephapirin sodium 25953-19-9, Cefazolin 26787-78-0, Amoxycillin 32388-53-7, Ampicillin monohydrate 33993-48-5, DL-Ampicillin 34444-01-4, Cefamandole 35607-66-0, Cefoxitin 38821-53-3, Cephradine 50370-12-2, Cefadroxil 50972-17-3, Bacampicillin 53994-73-3, Cefaclor 55268-75-2, Cefuroxime 58151-30-7 60925-61-3, Ceforanide 61270-58-4, Cefonicid 62893-19-0, Cefoperazone 63527-52-6, Cefotaxime **64544-07-6**, Cefuroxime axetil 64952-97-2, Moxalactam 68401-81-0, Ceftizoxime 69712-56-7, Cefotetan 72558-82-8, Ceftazidime 73384-59-5, Ceftriaxone 145430-98-4 145430-99-5 145454-26-8
(topical compns. contg., for acne treatment)

IT **64544-07-6**, Cefuroxime axetil
(topical compns. contg., for acne treatment)

L67 ANSWER 13 OF 13 USPATFULL
AN 91:90758 USPATFULL
TI R-**cefuroxime axetil**
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PA Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)
PI US 5063224 19911105 <--
AI US 1990-550005 19900709 (7) <--
DT Utility
EXNAM Primary Examiner: Rizzo, Nicholas S.
LREP Ashbrook, Charles W.; Whitaker, Leroy
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 444
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB R-**Cefuroxime axetil** which is substantially free of the S-isomer is readily absorbed from the stomach and gastro-intestinal track of animals, and is therefore ideally suited to oral therapy of bacterial infections.

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AB R-**Cefuroxime axetil** which is substantially free of the S-isomer is readily absorbed from the stomach and gastro-intestinal track of animals, and is. . .
SUMM This invention is directed to the preparation and use of the R-isomer of **cefuroxime axetil** in a form substantially free of the S-isomer.
SUMM . . . oral dosing. Crisp et al., in GB2,145,409A, describes the synthesis of the 1-acetoxyethyl ester of cefuroxime, now referred to as **cefuroxime axetil**. **Cefuroxime axetil** is a prodrug of cefuroxime which can be orally administered, thereby permitting more convenient and wider therapeutic use of cefuroxime. Unfortunately, **cefuroxime axetil** suffers from several deficiencies, including being rapidly hydrolyzed in the intestine, leaving substantial unabsorbable cefuroxime. Campbell et al., in Biochemical. . . 2317-2324, 1987, report the isolation and partial characterization of an esterase enzyme which is said to be responsible for converting **cefuroxime axetil** to cefuroxime in the gut. The ester portion of **cefuroxime axetil**, namely the 1-acetoxyethyl group, contains an asymmetric carbon atom at the 1-position, and accordingly **cefuroxime axetil** exists in the form of a mixture of the R- and S-isomers. Oral administration of the R,S-mixture of **cefuroxime axetil** results in only about fifty percent bioavailability of the cefuroxime antibiotic, due to low overall solutility and the rapid hydrolysis. . .
SUMM We have now discovered that the individual S-isomer of **cefuroxime axetil** is hydrolyzed in animals much more rapidly than the R-isomer. Accordingly, an object of this invention is to provide R-**cefuroxime axetil** substantially free of the S-isomer, and to provide a method for administering R-**cefuroxime axetil** and not administering the S-isomer. Such selective administration results in surprisingly greater bioavailability of cefuroxime, and thus dramatically reduces the. . .
SUMM This invention provides in substantially pure form R-**cefuroxime axetil** of the formula ##STR1## The invention further provides a pharmaceutical formulation comprising R-**cefuroxime axetil** substantially free of the S-isomer admixed with a conventional diluent or carrier therefor, and a method of treating bacterial infections comprising administering such substantially pure R-**cefuroxime axetil**. The invention additionally provides a method for preparing substantially pure R-**cefuroxime axetil** comprising selectively solubilizing such compound from a racemic mixture of R,S-**cefuroxime axetil**.
DETD According to one embodiment of this invention, there is provided R-**cefuroxime axetil** in substantially pure form. The term "substantially pure form" means R-**cefuroxime axetil** substantially free of S-**cefuroxime axetil**. A preferred compound is one in which such R-isomer is present in greater than about eighty-four percent, preferably about ninety percent or more, relative to the total R and S-**cefuroxime axetil** contained therein.
DETD The substantially pure R-**cefuroxime axetil** of this invention is prepared by selectively solubilizing the R-isomer in a solvent in which the S-isomer is only minimally. . . than the S-isomer. The R-isomer is surprisingly more soluble than the S-isomer in organic solvents such as ketones, for example **acetone** and methyl ethyl ketone, nitriles such as acetonitrile, esters such as methyl acetate and ethyl acetate, alcohols such as methanol,. . . ethanol, n-butanol and the like, and halogenated hydrocarbons such as dichloromethane, 1,2-dibromoethane, and chloroform. Generally, a mixture of R and S-**cefuroxime axetil**, prepared as described

in GB 2,145,409A, and containing the R and S-isomers, is added to a solvent to form a. . .

DETD The slurry mixture of RS-**cefuroxime axetil** in a solvent preferably is stirred or agitated at a temperature of about 24.degree. C. to about 90.degree. C. for. . . a period of time from about one-half hour to about ten hours. Such conditions facilitate solution of the more soluble R-**cefuroxime axetil**, while permitting the undesired S-isomer to remain suspended in the solvent. The precise time of agitation and temperature are not. . . phase is recovered and can be concentrated by removal of the solvent under reduced pressure, thereby affording the substantially pure R-**cefuroxime axetil** as a dry powder, generally amorphous. The product can be readily crystallized by conventional methods utilizing common solvents such as alcohols and the like. The R-**cefuroxime axetil** of the invention can be crystallized directly from the liquid phase by conventional techniques, for instance by cooling the solution. . . or by adding a suitable antisolvent such as diethyl ether, hexane, cyclohexane or the like. Absence of water provides crystalline R-**cefuroxime axetil** as an anhydrate, whereas addition of water provides the crystalline R-**cefuroxime axetil** hemihydrate. Alternatively, the manner in which the R-**cefuroxime axetil** is exposed to water can determine the crystal form produced. For example, if water is added to an **acetone** solution of R-**cefuroxime axetil**, the anhydrous crystal form is produced, whereas if an **acetone** solution of R-**cefuroxime axetil** is added to water, the hemihydrate crystal form is produced.

DETD As noted above, the surprisingly good solubility characteristics of R-**cefuroxime axetil** make it useful as an oral treatment for bacterial infections in animals. The R-isomer is readily absorbed in the stomach. . . before the esterase enzymes located there are able to hydrolyze the axetil portion of the molecule. Accordingly, oral administration of R-**cefuroxime axetil** results in good absorption of antibiotic from the stomach and gut, resulting in drug levels of cefuroxime in the blood. . .

DETD . . . embodiment of this invention is therefore a method of treating bacterial infections comprising orally administering an antibacterially effective amount of R-**cefuroxime axetil**. The compound is active against a wide range of gram positive bacteria, including Staphylococcus aureus, Streptococcus pyogenes, and Streptococcus pneumoniae, as well as gram-negative bacteria such as Haemophilus influenzae, Neisseria gonorrhoeae, Klebsiella pneumoniae, and Proteus mirabilis. As such, R-**cefuroxime axetil** is useful in treating lower respiratory tract infections such as pneumonia, urinary tract infections, skin and skin structure infections, septicemia, gonorrhea, as well as bone and joint infections, caused for example by S. aureus. R-**cefuroxime axetil** will be administered at an adult dosage of about 500 mg. to about 2.0 g. every eight to ten hours. . . treatment of infants and children, typically at dosages of about 10 to about 200 mg/kg per day. The substantially pure R-**cefuroxime axetil** is well tolerated by infants and children due to its acceptable taste characteristics.

DETD The substantially pure R-**cefuroxime axetil** of this invention can be formulated with any number of readily available pharmaceutical carriers and **excipients** for convenient oral administration. The compound will typically be formulated as a dry powder in a capsule, or molded into a tablet, or prepared as a syrup or suspension. Typical carriers and **excipients** which can be utilized include pharmaceutical carriers such as **lactose**, sorbitol, **mannitol**, starch, amylopectin, **cellulose** derivatives, calcium **stearate**, polyvinylpyrrolidone, and related pharmaceutical carriers and diluents. Suspensions and syrups can be formulated with water, glycerol, propylene glycol, vegetable oils,. . . The formulations provided by this invention will contain from about 0.5 to about 95.0% by weight of the substantially pure R-**cefuroxime axetil**, admixed with the pharmaceutical

carrier or diluent.

DETD Substantially pure R-**cefuroxime axetil**

DETD One hundred grams of a mixture comprised of forty-nine percent (as determined by high performance liquid chromatography) S-**cefuroxime axetil** and fifty-one percent R-**cefuroxime axetil** were added to 338 ml of methanol at 24.degree. C. The resulting slurry was heated to 60.degree. C. and stirred. . . C. and filtered. The solvent was removed from the filtrate to provide a powder identified by HPLC as 93% pure R-**cefuroxime axetil**, the remainder of which was S-**cefuroxime axetil**.

DETD R-**Cefuroxime Axetil** - Production Scale

DETD . . . was purged with nitrogen gas, and heated to 50.degree. C. To the warm methanol were added 173.2 kg of racemic **cefuroxime axetil**. The reaction suspension was heated at 60.degree. C. and stirred for one hour. The reaction slurry was then cooled to. . . reactor. The filter cake was air dried at 40.degree. C. to provide 102.2 kg of a white powder identified as S-**cefuroxime axetil**.

DETD . . . vacuum dryer in which it was dried at 40.degree. C. for 6 days to provide 63.0 kg of crystalline anhydrous R-**cefuroxime axetil**. The product was analyzed and shown to contain 85% by weight of R-**cefuroxime axetil** and 15% by weight of S-**cefuroxime axetil**. Microbiological assay demonstrated the product had 99% biological potency.

DETD To a round bottom flask containing 3.0 liters of methanol were added 789 g of racemic **cefuroxime axetil**. The mixture was a thick paste at 25.degree. C. but became a slurry when heated to 50.degree. C. for one. . . then filtered to provide a white powder that, when dried at 45.degree. C. under reduced pressure, afforded 342 g of S-**cefuroxime axetil**. The filtrate from above was concentrated to about 600 ml by evaporation of solvent under reduced pressure. The solution was. . . all solvents were removed by evaporation under reduced pressure to provide a dry powder identified as 362.5 g of crystalline R-**cefuroxime axetil** substantially free of S-isomer.

DETD X-Ray Pattern of R-**Cefuroxime Axetil**

DETD R-**Cefuroxime axetil** was prepared by the general procedures described above and recrystallized as follows. To 4.5 liters of **acetone** were added 150 g of substantially pure R-**cefuroxime axetil**. The solution was diluted by adding 15 liters of distilled water. The solution was stored at 5.degree. C. for several days, and the crystalline product which had formed was collected by filtration and identified as anhydrous R-**cefuroxime axetil**.

DETD The foregoing procedure was repeated, except the **acetone** solution of R-**cefuroxime axetil** was added to 15 liters of water. The crystalline product was collected and identified as R-**cefuroxime axetil** hemihydrate.

DETD The two crystal forms of R-**cefuroxime axetil** were x-rayed utilizing a Nicolet I2V Diffractometer having a graphite monochromator and measured at a wavelength of 1.5418 Angstroms.

DETD

Spacing, d (Angstroms)	Relative Intensities I/I max
X-Ray of R-**Cefuroxime Axetil** Anhydrate	
24.73	0.15
11.01	1.00
9.79	0.19
9.56	0.04
7.78	0.19
7.33	0.03
6.93	0.18
6.81	0.03
6.14	0.07

5.49	0.10
4.87	0.21
4.67	0.03
4.56	0.33
4.46	0.14
4.38	0.08
4.32	0.01
4.21	0.10
4.16	0.08
4.07	0.04
3.89	0.14
3.82	0.05
3.70	0.14
3.64	0.05
3.54	0.12
3.45	0.03
3.31	0.16
3.18	0.02
3.04	0.05
2.96	0.01
2.77	0.04
2.63	0.02

X-Ray of **Cefuroxime Axetil** Hemihydrate

12.21	0.10
11.69	0.23
10.71	0.38
9.65	0.44
8.52	0.40
8.14	0.05
7.44	0.51
7.03	0.32
6.88	0.37
6.55	0.09
6.32	0.17
6.10	0.16
5.58	0.68
5.43	0.35
5.35	0.15
5.01	0.09
4.85	0.61
4.70	0.37
4.65	0.20

4.51. . .

DETD The following study was conducted to establish that S-**cefuroxime axetil** is hydrolyzed to cefuroxime acid much more rapidly by esterase enzymes in blood serum than the R-**cefuroxime axetil** of this invention.

DETD A solution was prepared by dissolving 0.29 mg of R-**cefuroxime axetil** in 50 ml of Sorenson's phosphate buffer pH 7.4. Another solution was prepared by dissolving 0.26 mg of S-cefuroxime acetil. .

DETD Triplicate test tubes containing 2.75 ml of the R-**cefuroxime axetil** solution, and triplicate tubes containing 2.75 ml of the S-**cefuroxime axetil** solution, were each heated to 37.degree. C. and diluted with 0.25 ml of the serum preparation from above. Aliquot portions. . .

DETD The results of the above experiment establish that S-**cefuroxime axetil** is hydrolyzed much more rapidly in blood serum than the R-**cefuroxime axetil** of this invention. Accordingly, the compound of this invention has a longer half-life.

DETD The following experiment establishes that S-**cefuroxime axetil** is hydrolyzed much more rapidly in the dog gut than is the R-**cefuroxime axetil** of this invention.

DETD Following the general procedure of Example 2, 0.277 mg of R-**cefuroxime axetil** was dissolved in 50 ml of Sorenson's pH 7.4 buffer, and 0.263 mg of S-**cefuroxime axetil**

was dissolved in 50 ml of Sorenson's pH 7.4 buffer.

DETD Triplicate tubes of 2.75 ml of the R-**cefuroxime axetil** solution, and triplicate tubes of the S-**cefuroxime axetil** solution, were allowed to equilibrate to 37.degree. C., and then 0.25 ml of the intestine mixture from above was added. . . decanted to an autosampler for assay, utilizing a standard Bio-Rad protein assay. The assays were analyzed for unchanged R- or S-**cefuroxime axetil** and afforded the following results.

DETD Experiments similar to those of Examples 2 and 3 were conducted and form the basis for our conclusion that S-**cefuroxime axetil** is hydrolyzed about 25 fold faster than R-**cefuroxime axetil** in bood serum, and about 3 fold faster in intestinal preparations.

DETD EXAMPLE 7

Formulation of Pediatric Oral Suspension

Ingredient	Amount	
Substantially pure R-**cefuroxime axetil**	2.5	grams
Sorbitol solution (70% N.F.)	40	ml
Saccharin	20	mg
Cherry flavor	50	mg
Distilled water q.s.	100	ml

DETD The sorbitol solution is added to 20 ml of distilled water and the R-**cefuroxime axetil** is suspended therein. The saccharine and flavoring are added and dissolved. The volume is adjusted to 100 ml with distilled water. Each ml of syrup contains 25 mg of R-**cefuroxime axetil**. This oral formulation is ideally suited for pediatric use.

DETD EXAMPLE 8

Preparation of 1.0 g capsule

Ingredient	Amount	
Substantially pure R-**cefuroxime axetil**	1.0	grams
Lactose	200	mg
Corn Starch	100	mg
	1.3	g

CLM What is claimed is:

1. Substantially pure R-**cefuroxime axetil**.

3. A process for preparing substantially pure R-**cefuroxime axetil** comprising adding an amount of a mixture of R and S-**cefuroxime axetil** to an amount of solvent in which the S-isomer is much less soluble than the R-isomer, said amount of solvent. . . equilibrium is reached, separating the liquid and solid phases, and removing the solvent from the liquid phase containing substantially pure R-**cefuroxime axetil**.

7. Crystalline R-**cefuroxime axetil** anhydrate substantially free of S-**cefuroxime axetil** and having the following x-ray pattern:

Spacing, d (Angstroms)	Relative Intensities I/I max
24.73	0.15
11.01	1.00
9.79	0.19
9.56	0.04
7.78	0.19

7.33	0.03
6.93	0.18
6.81	0.03
6.14. . .	

8. Crystalline R-**cefuroxime axetil** hemihydrate substantially free of S-**cefuroxime axetil** and having the following x-ray pattern:

Spacing, d (Angstroms)	Relative Intensities I/I max
12.21	0.10
11.69	0.23
10.71	0.38
9.65	0.44
8.52	0.40
8.14	0.05
7.44	0.51
7.03	0.32
6.88. . .	

IT **64599-28-6P**, R-Cefuroxime axetil
(prepn. of, via recrystn. of diastereomeric mixt. from methanol)

IT **64599-28-6P**, R-Cefuroxime axetil
(prepn. of, via recrystn. of diastereomeric mixt. from methanol)